GENETICS AND
THE INHERITANCE OF
INTEGRATED NEUROLOGICAL
AND PSYCHIATRIC PATTERNS

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VOLUME XXXIII

Editors

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A list of the previous issues in the Series of Research Publications will be found on verso of title page

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PREFACE

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The decision of the Trustees to present the subject again at its Thirty-third Annual Meeting was a wise one, but it placed a heavy burden upon the Program Committee because of the many aspects of present-day knowledge in this field from which only a relative few could be selected for presentation. The sequence finally adopted and presented in this volume places initial emphasis on the latest information concerning the principles of genetics and the methods of operation of genetic factors, with enough data on some abnormal states to indicate that all congenital conditions are not necessarily of genetic origin.

The papers on selected neurological and psychiatric conditions in which genetic factors play a role are preceded by a consideration of the normal inherited behavior patterns of man and other animals and their underlying morphological and physiological substrate.

Although only a segment of the field is here presented, it is hoped that some measure of continuity may have been given to the aspects under review.

December 18, 1953

DAVENPORT HOOKER

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Part I

GENETICS, HUMAN INHERITANCE AND ENVIRONMENTAL EFFECTS

CHAPTER I
PRINCIPLES OF HUMAN GENETICS

PAUL R. DAVID AND LAURENCE H. SNYDER[1]

The development of the science of medicine during the first half of the twentieth century has been phenomenal. At the present time this growth is continuing unabated, but gradually the emphasis is shifting. In the past, the attention of those most concerned with the progress of medicine has been chiefly directed towards the alleviation and control of unfavorable and deleterious agencies of the environment, such things as infectious agents, malnutrition, trauma, emotional stress, and occupational hazards.

Within the lifetime of many physicians practising today, the control of numerous noxious environmental agents has been achieved, or at least has become a practical possibility. During this same interval, however, there has been developing a science relating to the human host which may well contribute prominently toward a shift of emphasis in our approach to problems of the treatment and prevention of disease. This discipline is genetics. It has often been defined as the study of heredity, but in its more modern sense it is better described as the study *of the origin*, development and distribution of individual differences.

Heredity can not operate in a vacuum, and we can not hope adequately to understand the action of hereditary factors in the development of any trait, pathologic or normal, except in the framework of the environment in which the factors attain expression. Knowledge of the extent to which genetic factors are involved, and of the mechanisms through which they are expressed, is essential to a complete understanding of the natural history of any disease.

A priori considerations derived from principles of evolution genetics lead to the prediction that, when hereditary factors are the exclusive or nearly exclusive determinants of a severe disease, the disease is likely to be a rare one, and the roll call of obscure conditions which provide the bulk of textbook illustrations of clearly inherited pathologic conditions in man amply confirms the prediction. But the unlikelihood that hereditary factors are exclusive determinants of the commoner disorders does not justify our slighting the investigation of their possible significance as causal components.

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Half a century of genetic investigation since the rediscovery of the Mendelian laws has amply demonstrated that the basic principles of genetics insofar as they relate to mechanisms of hereditary transmission or to the action of hereditary factors in development are in essence the same in all sexually reproducing organisms whether men or mice bread molds or butterflies

Nevertheless there are important differences between the genetics of man and that of laboratory or domestic animals One which will at once occur to you derives from the uniqueness of the human animal in respect to cerebral development and social organization From this you might properly *expect to find the interactions between hereditary and environ*mental factors especially in the development of behavioral patterns far more complex and far subtler than in any other creature

An equally important difference is that between the kinds of variations which for sound historical reasons have received most prominent attention in the laboratory and the kinds of variations which may be most significant in the variability of natural populations It may seem paradoxical to refer to populations of civilized man living under the highly artificial conditions of an electronics era as *natural* but in respect to genetic structure human populations have much closer resemblance to populations of field mice foxes or even fruit flies living in the wild than to herds of dairy cattle flocks of domestic poultry or to laboratory stocks of mice or guinea pigs

We *shall* of necessity discuss principles *of human genetics within the* framework of knowledge derived from experimental genetics but we shall try especially to call attention to those particulars in which human material requires special treatment

The principles of genetics as we know them today have largely emerged from investigating the effects of *gene* differences among individuals and the *distribution* of gene differences both among the progeny of various kinds of matings and in the population at large

It is a familiar observation that no two organisms whether of our own species or of any other are completely identical either in physical appearance or in the details of their physiologic processes Insofar as individual differences have an hereditary basis they have been found to be contingent predominantly upon materials carried in the chromosomes Following the discovery of genetic linkage early in this century the mapping of chromosomes became possible and was accomplished on an appreciable scale first and most spectacularly in Drosophila and later in a variety of forms both plant and animal This work showed without equivocation that in innumerable instances hereditary differences could be referred to minutely localized regional differences within *the chromosomes* each

having a linear extent of less than one fiftieth of a micron—well below even the theoretical resolving power of an optical microscope These are *gene* differences

We are often inclined to think of genes as discrete particles strung along each chromosome much like beads on a string It is probably better to conceive of them as regional differentiations of the chromosomes Thus, the difference in *genotype* or genetic constitution, between a color blind man and a man with normal color vision is a difference, perhaps an intra molecular rearrangement in a particular region or *locus* of their respective X chromosomes the genotypic distinction between a hemophilic and a non hemophilic lies in a difference between their respective X-chromosomes at another locus

When two or more modifications of the same gene exist, any *one* of which may occupy a given locus on a particular chromosome, they are said to be alleles of one another, a technical way of saying that they are alternatives Thus we may speak of the normal allele of the protanopia gene or the normal allele of the hemophilia gene If you possess neither the protanopia gene nor the hemophilia gene on your X-chromosomes, their places are occupied by their respective normal alleles

We commonly refer to color blindness (as contrasted with normal color vision) or to hemophilia (as contrasted with the non hemophilic condition) as the effect of a single gene substitution or more briefly, as the effect of a single gene The expression is inexact but very convenient You may recall that in many species including man, each cell of the male contains only *one* X *chromosome*, while there are two X chromosomes in the female, all other chromosomes (the so-called *autosomes*) are in both sexes present in matched or homologous pairs and in each chromosome of an homologous pair is found the same series of *gene loci* Consequently, an autosomal gene such as the gene for albinism may be *present on only* one member of a pair of homologous chromosomes in which case it is s[illegible] in *hetero*

[illegible] single [illegible]tution will be *understood* to mean a gene substitution *of a single locus* in whichever dosage (heterozygous or homozygous) is necessary to produce a discernible effect

Among the facts that have been learned about single gene substitutions we may note the following as particularly pertinent to human genetics

(1) There is not as was originally supposed by many, necessarily a one to-one correspondence between the presence of a gene and the mani festation of an effect The organism is not a mere mosaic of unit char

acters. Wholly aside from environmental influences (to be considered presently) an animal's phenotype depends on developmental interactions involving the entire aggregate of genic material together with the materials of the extra-genic protoplasm. There are indeed some single gene substitutions with regularly manifested effects regardless of what other genes may be present in the residual genotype. The genes responsible for differences in the various *blood group antigens in man apparently are in this* category. In other instances there is clear cut interaction between two individually identifiable single gene substitutions. Thus in Drosophila the genes scarlet and brown individually are responsible for eye colors corresponding to their respective names. The eyes of a fly possessing both these genes are, however, white (Wright 52). In contrast to this very simple type of interaction there are countless instances in which the *effect of a single gene substitution may be conspicuously altered by an* accumulation of numerous other genes (modifiers) which themselves do not have any readily discerned individual effect at all. The gene for myelencephalic blebs in house mice is one of many in this category. The effects of this gene include agenesis or atrophy of the eye and its adnexae and various malformations of the forelimbs, hindlimbs, or both. By selective breeding for the accumulation of different sets of modifying genes, however, it has been possible to develop stocks among which the manifestation of the myelencephalic bleb gene differs markedly: in one such stock there are almost no limb defects but many eye defects; in another more than 90% of the animals exhibit *both* limb and eye defects; in a third, the mice are practically free of *any* anomalies. In each of these stocks all animals are *homozygous for the myelencephalic bleb gene.* The differences depend on the different accumulations of modifiers (27).

(2) A second important principle of gene action is that the phenotype of an organism is, in general, a resultant of interactions between genotype and environment. Different genes vary greatly in their responsiveness to environmental alterations. The effects of some are expressed with consistent uniformity under any environmental *conditions that permit the organism* to survive at all. The genes for the human blood group antigens may again serve as illustration. At the other end of the scale we find genes which produce effects readily distinguishable from those of their alleles only when a very specific environmental factor *is present*. Thus rabbits possessing the "white fat" gene have fat which is colorless regardless of their *diet*. Rabbits homozygous for the allele of this gene ordinarily have yellow fat, but on a xanthophyll-free diet their fat is also white (18). That is, the two genotypes are indistinguishable unless xanthophyll is present in the diet.

Examples of this sort, which could be multiplied at considerable length

should readily dispose of the recurrent fallacy that if an abnormality or a disease is hereditary it therefore cannot be amenable to treatment. It would seem plausible that severe pathologic conditions contingent upon regularly manifested single gene substitutions would be relatively unlikely to respond to therapy. But we have at least substantial hints of effective treatment for a few human pathologic conditions in which single gene substitutions are etiologically involved. Thus splenectomy appears to prevent recurrence of hemolytic crises in hereditary acholuric jaundice, posterior pituitary extract is often helpful in those cases of diabetes insipidus which appear to be contingent on a dominant gene of nearly if not quite, regular manifestation.

(3) A third principle, intimately related to the last, is that in many, and perhaps in all cases, the effects characteristic of a given gene can be induced by environmental factors acting at an appropriate time during development in the absence of the gene in question. In Drosophila, *phenocopies* of nearly every known single gene effect have been produced by heat shocks of varying duration and intensity (17); in mice, X radiation at specific embryonic ages has yielded congenital anomalies of various types, several of which are known otherwise to occur as gene effects (38); in poultry, phenocopies have been produced by various treatments of the early embryo (1, 24, 53).

(4) As a fourth generally important principle, we must recognize that superficially indistinguishable effects may be produced by quite different gene substitutions, that is, by genes at different loci. Several cases of such mimic genes are known in mice (e.g., *Shaker 1* and *Shaker 2*, with gene loci on different chromosome pairs, both are characterized by deafness, choreic head movements, and circling behavior).

Mimic genes are doubtless common in man, but are often likely to escape identification as such unless they exhibit different patterns of transmission. It is, in fact, quite the rule in human material to find in some families an autosomal dominant gene, in others an autosomal recessive, and in still others a sex linked recessive responsible for more or less indistinguishable variants (differing sometimes in age of onset and in severity) of a single clinical entity (e.g., retinitis pigmentosa, peroneal atrophy, progressive muscular dystrophy). It should be recognized that the results of therapeutic trials on one of these genetically different categories need not necessarily be applicable to others. An instructive case in point is found in Drosophila.

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effect on cinnabar or scarlet larvae (19) *On the other hand* the pigment abnormality contingent upon the cinnabar gene may be remedied by treatment of cinnabar larvae with 3 oxy kynurenin (9) which would not be expected to affect eye color development in scarlet flies Now the vermilion gene is sex linked, while cinnabar and scarlet are autosomal, vermilion is therefore readily distinguished from either of the latter genes by its different pattern of transmission Cinnabar and scarlet however since they are both carried on autosomes both exhibit the same pattern of transmission although their closely similar effects are produced by different developmental mechanisms which respond differently to preventive treatment'

The moral of this for human genetics would seem to be clear in undertaking the study of a gene contingent pathologic condition, we need to look carefully for evidences of genetic heterogeneity even among those families in which the general pattern of transmission is the same If several *variant forms of a pathologic condition are all manifestations of the same* gene acting in different cases under the influence of different modifying factors we would reasonably expect that the same preventive or therapeutic treatment might be to some degree effective for all of them If the variant forms are contingent upon different genes, different treatments might be required

It must be evident from the foregoing that genetic constitution may be involved in the etiology of human abnormality and disease in diverse ways and in widely varying degree

There are in man, as in experimental animals a number of pathologic or conspicuously abnormal conditions contingent upon single gene substitutions with regular manifestation independent of residual genotype and of environmental variables Among the aberrations of which the bulk of cases can safely be attributed to single gene substitutions of this type are sickle cell anemia thalassemia juvenile amaurotic idiocy phenyl ketonuric amentia and hemophilia (attributable to one or another of several single genes perhaps mutually allelic) Not a great many more could be added to this list if we restrict ourselves to those conditions for which *systematically* assembled material exists in reasonable mass

In a larger number of pathologic conditions in man the familial cases appear to satisfy the statistical requirements of single gene hypotheses but we find an excessive proportion of sibships with only single members affected In these instances the familial cases may be attributable to a regularly manifested single gene substitution or to one or another of several such substitutions at different loci An appropriate fraction of the sporadic cases must also be so determined but a substantial proportion must have other causes In this category we would include retinitis pig

mentosa (see Usher's pedigrees in Bell 5, congenital deafness, 21, 29, split hand 7 progressive muscular dystrophy, 25, 39, 49, 50, and Herndon and David unpublished) and very probably diabetes insipidus (26) Microcephaly may also belong here, as Penrose (35) has suggested, although no systematic collection of sibships has been published, cerebral palsy probably does not at least when associated with amentia there appears to be significant familial aggregation, but in Penrose's series, at least, the familial incidence in the sibships with more than one affected is too low to fit any simple Mendelian expectancy

A third way in which single gene substitutions may be significant in the etiology of human disease is illustrated by conditions contingent upon genes with variable manifestation (45) These can usually be identified without serious difficulty in laboratory animals, but in human material the identification of the genetic mechanisms involved is likely to be difficult or nearly impossible Exceptions to this rule would be chiefly of two kinds

(1) Conditions reflecting the manifestation of a dominant gene with relatively high penetrance (frequency of manifestation), say minimally 80% or 90% Retinoblastoma is doubtless in this category

(2) Conditions in which the pathologic manifestation is only the occasional expression of a gene the presence of which can otherwise be detected by other less serious but more regularly manifested effects Some pedigrees of dystrophia myotonica may belong here A gene is apparently involved which may be expressed as myotonic dystrophy with or without a highly characteristic type of cataract or as cataract alone One or the other of these aberrations appears to be manifested in almost every individual who possesses the gene although the cataractous changes may be so slight as to be demonstrable only by slit lamp examination (51)

In addition to conditions in which single gene substitutions may be etiologically implicated in one of the above ways there are many diseases both infectious and non infectious which appear to have some predisposing genotypic basis that may not be analyzable in terms of the single gene differences of classical genetics Presumably the distribution of these diseases reflects complex interactions between environmental variables and genotypic variation which is probably *polygenic* The single genes we have been discussing so far (except for the genetic modifiers mentioned in an earlier section) are called *major genes* in contradistinction to *polygenes* a term designating genes with *individually imperceptible* effects (31)

Major gene effects usually involve readily discernible phenotypic discontinuities In laboratory animals at least and to some extent in man they can be individually identified by the discontinuities they produce and can be assigned with varying degrees of precision to specific loci on one or another chromosome In contrast polygenes do not individually

produce discernible discontinuities. They tend to have quantitatively equivalent cumulative effects, and they cannot be individually identified and assigned to chromosomal loci. Their reality is hardly to be doubted, however, in view of the effectiveness of selective breeding for almost any continuously variable character in a genetically heterogeneous population of laboratory or domestic animals; and Mather has adduced what he regards as critical evidence that polygenes exhibit essential characteristics of classical genes, viz., segregation and crossing over.

We have elsewhere (12) argued that by far the greater portion of phenotypic variability in normal human traits, insofar as it is genotypically determined, may depend on polygenic differences rather than on major gene effects. We suspect that this conclusion is also applicable to that portion of the range of *pathologic* variability which includes the bulk of the *commoner* human disabilities for which there may exist any appreciable individual differences in genetic predisposition. The only well authenticated major gene effects with frequencies of from 5 to 50 per cent in human populations are, as far as we know today, those which are approximately neutral in their effects on viability. Of the hundreds of presumptively single gene abnormalities which are of a more or less serious pathologic nature, very few have frequencies higher than one in 5000 and the vast majority are rarer than 1 in 20 000. These observations would lead us to suspect that any genetic differences in predisposition which may exist for the commoner diseases are likely to involve either major genes which are incompletely penetrant in respect to their pathologic manifestations, or else (and perhaps more often) they will be found to rest upon polygenic variability.

If the inference just suggested has any validity, it is obvious that its methodologic implications are considerable. Let us, for example, consider just two simple questions:

(1) What observational data are necessary and sufficient to establish that genetic constitution is of etiologic significance in the case of a given disease?

(2) If our data convince us that genetic factors have *some* etiologic importance, *how important are they* in comparison with nongenetic variables?

We have said that these are simple questions; that does not mean we believe the answers to be simple, and in any case we shall not attempt to answer them definitively. Indeed they may not even have any altogether satisfactory answers; but if this be the case, it would be desirable to recognize it.

Our first question was: What are the necessary and sufficient criteria for establishing that genetic constitution is significant in the etiology of a disease?

For the identification of conditions dependent on single gene substitu-

tions with regularly manifested pathologic effects it has been more or less tacitly agreed that the postulated single gene mechanism is plausibly demonstrated if the following criteria are met (a) statistical agreement with Mendelian expectancies in respect to familial incidence (19) and population frequencies (6 11, 41) (b) complete concordance in monozygotic twin pairs and (c) either an elevated rate of parental consanguinity, in the case of presumed autosomal recessive determination (when the condition is rare) or appropriate pedigree patterns for presumptive dominant or sex linked transmission

Tests of this type are of course almost or entirely useless for establishing the significance of genetic factors in conditions which are etiologically more complex than those contingent on regularly manifested single gene substitutions There are other statistical tests to be satisfied when a more complicated mechanism is suggested—as for example dependence on a single gene with incomplete penetrance here there are predictable relationships between the frequencies of the condition among sibs *parents*, children and other cognates of affected individuals and the relationships differ according to whether the gene involved is dominant or recessive, and according to its degree of penetrance and its frequency in the population But while these tests provide *necessary* criteria which must be satisfied *if a* genetic mechanism of the type specified is to be inferred it does not answer [illegible]

[illegible] collected and admirably *reported* by Fogh Andersen (15) This malformation is more favorable for genetic investigation than are many pathologic conditions *in man* first, because it is readily diagnosed and second because it is *present* at birth Moreover, it is not excessively rare and Fogh Andersen s material relating to 703 propositi is one of the half dozen or so largest series of systematically assembled familial incidence data extant also it includes what is probably quite reliable information *on parents* aunts and uncles of the propositi and a limited amount on grandparents and children

Now the data from this study appear to be consistent, *in* all respects in which they can be tested with the author s *suggestion* that the malformation may depend in most or all of the *families* in the sample on a single *gene* which may be fully penetrant *in* homozygotes and is occasionally (and with different frequency in the two sexes) *manifested* when heterozygous Penetrance in heterozygotes *would* be roughly *in* the range of 5% to 15% The author recognizes that other possibilities exist however and in fact the data would appear to be consistent also with an hypothesis that a commoner gene is involved manifested only when homozygous and then exhibiting a penetrance roughly double that *required* for the irregular

dominant hypothesis The data are also consistent with any mixture of these hypotheses, or perhaps, of these hypotheses and still others —heterogeneity cannot be demonstrated in the material but neither can it be excluded If twice or ten times as many data were available, it is quite possible that heterogeneity could be shown to exist and it is probable that one or more of the interpretations with which the *current data are consistent could* be ruled out by goodness of-fit tests But it is hardly conceivable that every possible or even plausible genetic interpretation could be thus excluded, because of the very considerable flexibility of genetic hypotheses beyond those of the very simplest type

The preceding considerations would seem to suggest that a good fit between observed data on the distribution of a pathologic trait and the statistical requirements (even though these may be manifold) of one or another hypothesis of genetic mechanism may be not only insufficient to establish that the mechanism in question is actually the one involved, it may not be sufficient even to establish that genetic factors are significantly involved *at all*

On what basis, then, may we be permitted to conclude, in the case of harelip, or for any other pathologic condition in man, that genetic factors are etiologically significant even if we are unable to specify the precise patterns of transmission involved? In other words, how can we be convinced that the development of the condition is, in some or all cases, dependent on the presence of genotypes not universally characteristic of the species?

It is usually felt, with certain reservations, that examination of systematically collected twin data can give a decisive answer to this question If the concordance frequency in monozygotic twin pairs is significantly higher than in dizygotic pairs, we infer that genetic factors have an etiologic role *In general*, the inference would appear to be valid, if the basic assumption of the concordance-discordance method can be shown to apply this assumption is, of course, that *average intra pair differences in all environmental factors which could possibly have etiologic relevance are substantially the same for both types of twins* The assumption is often open to grave question, especially when psychologic traits are the subject of investigation, but in all cases, it should be remembered that its validity is something that needs to be substantiated, not taken for granted

In the absence of adequate twin data, the question of the etiologic implication of genetic factors can also be answered with some degree of assurance from data on the incidence of the condition among sibs and other relatives of affected propositi, as compared with the incidence in a control population Here also, essentially the same reservation must be made as for the twin studies An incidence significantly higher than that in the general population can be taken as substantial evidence that genetic factors are

etiologically involved, but only if it is shown that environmental factors cannot account for the increased incidence. This may be attempted in more than one way. Comparison may be made with the general population, if it can be reasonably established that the propositi are not disproportionately drawn from environments which may include factors of conceivable etiologic relevance to the condition under investigation. Or comparisons can be made with relatives of a control group. The controls must then be comparable to the group of propositi as nearly as can be in respect to all factors in the environment which may conceivably affect the incidence of the condition.

In the case of harelip it is possible for Fogh-Andersen (and for us with him) to be reasonably satisfied that genetic factors have an etiologic role on the basis of the accumulation of cases among relatives of propositi. Unselected twin data for this anomaly are too scanty to be statistically convincing but they point in a confirmatory direction. The likelihood that something in the physiologic status of mothers who bear harelipped children may account for the familial incidence can be largely ruled out: the frequency of the condition is significantly above population frequency, and to about the same degree, among paternal as well as maternal cognates of the propositi. The possibility that undefined ecologic factors may account *for the high incidence of the condition among sibs and other cognates alike must* also be considered. This possibility is diminished by Fogh-Andersen's examination of the social-occupational classes, geographic origins and habitat (rural or urban) of his cases. In all respects noted they appeared to conform reasonably well in their distribution to the Danish population as a whole. *Only because these investigations were made* are we permitted to regard the familial aggregation data as reasonable evidence for the significance of genetic constitution in the etiology of harel

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th ... *at the cogency of data on familial incidence or on twin concordance as evidence for the significant implication of genetic factors in the etiology of a disease rests ultimately upon the exhaustive ness with which it has been possible to exclude environmental factors as responsible for the associations found.*

It goes without saying that absolutely exhaustive exclusion of all environmental factors that might be relevant is at best an as ...
sibility which ca ... be ...
suffers both fro...
tion. But it is nc ... cism because of the unattainability of absolutes: for in all areas of our behavior we are constantly forced to be satisfied with something less than absolute certainty, and to accept

and act upon, provisional certainties What we do want to stress is what we conceive to be the positive implication of our discussion

The essence of it is that studies of familial incidence, or of aggregation among cognates, *aimed at discovering the etiologic significance of genetic* factors in a disease are not in themselves adequate They should, in general, be integrated with investigation of the distribution of the disease in relation to as many ecologic factors as it is practicable to take cognizance of Clemmesen (10) and others have repeatedly stressed this point in relation to genetic studies of cancer, and we hope its importance is evident, not only for cancer studies, but for investigations of virtually any disease, whether infectious or organic degenerative Our urging this point so vigorously must not be taken to reflect adversely on the many careful studies of familial incidence, twin concordance, and the like, which from limitations of practical necessity have had to forego the inclusion of ecologic data The inferences which can be drawn from findings in these studies were restricted by the limitations of method, they nevertheless may serve as valuable pilot studies, providing information which later can be supplemented by and collated with data of other kinds By the same token, such studies as those of Herrington and Moriyama (20, 32), are of value to geneticists, even though they contribute no genetic data They provide information on the *correlation of climatic, geographic, socio economic, and other ecologic variables* with mortality from a number of diseases Information of this type can provide much needed guidance for geneticists by suggesting the ecologic variables *which most obviously require attention in genetic studies*

The second question we proposed to consider was "If our data convince us that genetic constitution has some etiologic importance, *how* important may we say it is, in comparison with non genetic factors?" The question, without qualification, has little meaning, because the word 'important' is itself equivocal In this context, there are at least three ways in which 'important' might be interpreted

(1) The relative importance of genetic and environmental factors might be assessed in terms of the fraction of total trait variability for which each is responsible This is clearly a matter of great interest to the geneticist A knowledge of the statistical share of responsibility for the distribution of a disease which might be allocated respectively to the environmental and to the genetic components in its etiology would seem to offer promise of being helpful as a guide towards the most economic methods of control We must confess, however, that efforts to make such an allocation are beset with pitfalls, including the problem of taking interaction into account, as was recently noted by Eysenck and Prell (14) in their attempt to evaluate the role of hereditary factors in neurotic personality

In this connection it should be observed that the relative concordance

values found in monozygotic and dizygotic twin pairs respectively, contrary to a common belief do not permit an estimate of the *degree* to which genetic determination is involved in the trait under consideration. As an extreme illustration, monozygotic twin pairs are, of course, 100% concordant with respect to blood group O while dizygotic pairs are only about 70% concordant. With respect to blood group AB, however, while there is again 100% concordance in monozygotic twins, there is only about 30% concordance in dizygotic pairs. Yet genetic determination is complete in both instances.

In fact, from studies which are restricted to a comparison of trait concordance in twin pairs alone the valid inferences that can be drawn appear to be very limited in number, though not in importance.

We can state that there must be 100% concordance in monozygotic twin pairs for a condition exclusively determined by hereditary factors. The converse, however, is not equally true, that is, 100% concordance among monozygotic pairs does not necessarily mean exclusively genetic causation. On the other hand, anything less than 100% concordance among monozygotic pairs does permit us to *exclude* genetic factors as sole determinants. Finally, if there is the *same* per cent of concordance in monozygotic as in dizygotic pairs, we can rule out genetic factors altogether. All other possible findings can tell us only that both genetic and environmental variables are or may be etiologically involved.

By extending twin-concordance studies to include incidence data [illegible] made unless material is drawn from a representative range of environmental situations and is classified in respect to what may be significant ecological variables.

The addition of data regarding sibs and other relatives is, however, important, because a comparison of incidences in the three groups, monozygotic twins, dizygotic twins, and sibs, will indicate in most cases the general direction in which we should look for etiologically significant environmental factors. With *monozygotic concordance* less than 100%, a lower incidence among sibs than among dizygotic co-twins suggests that the environmental factors of *primary relevance* are those for which the *intra-familial* variability is likely to be greater than the variability *between* families, for example, prenatal influences associated with maternal age, or exposure to an epidemic disease of relatively long cycle and narrow age range of susceptibility.

An *equivalent* incidence among sibs and dizygotic co-twins together with less than 100% concordance in monozygotic pairs, on the other hand, points to the implication of ecologic factors of the sort which are likely to

be relatively constant within the family, but which may vary considerably between families, for example the level and quality of nutrition, occupational *and housing conditions, and* so on.

(2) The importance of genetic constitution as an etiologic factor in a disease might be evaluated in terms of the morbidity risk for persons of specified degree of relationship to index cases, as compared with the risk for unrelated individuals This *is a sense in which the word 'importance'* has very real meaning for the close relatives of patients with severe neuropsychiatric disorders, for example

Thus, the data of Kallmann and Reisner (23) on pulmonary tuberculosis suggest that the tuberculosis expectancy rate among sibs of index cases may be around 20 times the general population expectancy adjusted for age, sex, and race But the increased rate seen in this comparison obviously cannot altogether be attributed to genetic relationship, factors of exposure and of socio economic status are also involved The effects of these factors can be partially eliminated by comparing expectancy rates for sibs with those of husbands and wives of index cases In terms of this comparison, the tuberculosis risk for sibs of tuberculous individuals appears to be somewhat less than four times the risk for the genetically unrelated spouses (37) *Kallmann's well known twin-family study on schizophrenia (22) permits* similar comparisons, as well as the comparisons it was primarily designed to provide

(3) A third sense in which etiologic factors may be compared relates to problems of disease prevention For dealing with these problems, that etiologic factor which is most susceptible to control might be regarded as the predominantly important one In some infectious diseases, elimination of a vector has been found to be the most effective means of control, in others the best attack may be directly on the infecting organism, in still others, the establishment of host resistance through immunization is the most effective line of attack It seems to us that what might be called the direct control of genetic factors, through eugenic measures, is likely to have very limited utility (For a discussion of some aspects of this question, see *Snyder, 44, chapter 29*)

Indirectly however, the investigation of genetic factors in disease can, we are convinced be of inestimable value from a practical, as well as a theoretical point of view That knowledge of genetic factors can be of more than occasional utility in diagnosis, in genetic prognosis, in prevention and in other ways has been pointed out by Snyder (42, 43) and by others (28, 34, 46) In a still broader way we believe genetics will contribute to the control of disease through the influence of genetic thinking on investigative approaches in medical research which is aimed at disentangling the various etiologic *factors in disease* and at understanding the processes of patho-

genesis It goes without saying that knowledge of these factors and processes must in general tend to facilitate the discovery of methods of control

Essentially, the approach of the geneticist to problems of etiology and pathogenesis calls for the focusing of attention on the family group (or sometimes on a wider group of relatives) rather than on the individual patient in the traditional medical manner Something analogous to this has long been commonplace in the epidemiologic study of contagious diseases, of course But recognition of the fact that there is likely to be some genetic component in the etiology of almost any disease prompts us to look among the immediate relatives of diseased individuals for precursory signs or subclinical manifestations of the disease, and for morphologic stigmata or metabolic peculiarities which may be indices of susceptibility or predisposition More and more medical research on the organic and degenerative diseases is proceeding along these lines and although the approach is relatively new there is already ample evidence of its prospective value We may cite in this connection the abnormally elevated serum uric acid levels found among relatives of patients with gout, the reduced glucose tolerance among relatives of diabetics, the significantly high frequency of precocious achlorhydria in the families of pernicious anemia victims and the abnormal electroencephalographic patterns in parents and sibs of epileptics (33 40 48)

Particularly striking are recent genetically oriented investigations which give promise of clarifying the relationship between abnormal lipid metabolism and coronary artery disease Boas Parets and Adlersberg (8) found that approximately half of the sibs of 50 patients with coronary artery disease beginning before the age of 50 had abnormally high serum cholesterol levels (cf 47) The e patients were unselecte l except f ... patients known to be members of h ... ing on the e an l related findings ... (30) sugge t that the hope of reducing the incidence of atherosclerosis in persons with disordered cholesterol metabolism may lie in the early detection of the disorder We may suggest further that even more hope may conceivably lie in the discovery of abnormalities preceding the hypercholesterolemia

Other studies indicate an abnormal prevalence of hyperuricemia in families in which there is hypercholesterolemia (2) ... known ... of lipo ... pears t ... uent of coronary artery disease than the existence of either anomaly by itself (16) Adlersberg (3) has suggested that primary cholesterol lipoidosis may reflect a disturbance in genetically determined enzymatic chain reactions leading to the accumula

tion of lipid substances in the blood and tissues. The observations just cited indicate that we should perhaps look for a prior disturbance in an enzyme system which may underlie abnormalities in the metabolism of both purines and lipoids. These suggestions are quite in line with modern biochemical concepts of gene action in relation to metabolic abnormality.

The growing tendency to refer more and more diseases primarily to enzymatic dysfunction points up the value and even the urgency of research on the relationship of enzymes both to chromosomal genes and to plasmagenes. Recent studies indicate the possibility of including mitochondria and microsomes in the category of plasmagenes, and in any event these cytoplasmic inclusions are intimately bound up with the localization of certain enzymes (36).

Mutations in plasmagenes, and the comparatively inexact distribution of such bodies from a cell to its daughter cells as compared with chromosome distribution, may have important implications in the etiology and the genetics of disease, since these phenomena now appear to provide plausible bases for cellular differentiation as well as for variations in normal metabolic processes.

Moreover, the intimate interactions of hereditary and environmental influences, of which we have become increasingly aware in the development of all traits and characteristics, now appear to be of comparable importance in the ultimate physiology of the cell itself. It would appear that the gene may be responsible for the patterns for the production of pure protein enzymes and for the protein cores of more complicated enzymes, but that the co-enzymes are vitamin in origin. It is possible that hormones also may eventually be found to be sources of co-enzymes.

It may be that the clear one-to-one relationship between gene and enzyme which appears to exist in Neurospora (4) is so precise because the mold can synthesize all the amino acids and all the vitamins except biotin. In man, who requires many vitamins and amino acids, simple protein enzymes may be expected to be correlated with genes in a relatively simple manner, but the availability of co-enzymes is probably readily affected by nutrition.

A further implication of these considerations lies in the fact that in general there appears to be no way of getting an enzyme into a cell except by building it there. Thus, while the lack of certain enzymes may be due to improper nutrition or to the effects of inhibitors, there may well be a residue of diseases resulting primarily from gene-controlled absences of the basic patterns for requisite potent enzymes, for which there is no readily available cure in the usual sense.

It is, however, of prime importance to intensify the study of biochemical processes both in normal and in pathological development. It is possible

that some inhibiting actions which prevent the formation of potent enzymes are gene determined. But inhibitors, working perhaps through hydrogen ion concentration, inorganic ion strength, temperature, substrate concentration, oxidation reduction potentials and the like, *whether gene-determined or not*, may be subject to environmental control.

The search for precursory metabolic and other aberrations in the places in which they are most likely to be found, namely among the relatives of diseased individuals, may be expected not only to shed light on the mechanism of disease production, but to uncover those preclinical anomalies and constitutional stigmata which may suggest possible avenues for prevention and early control, either environmental or genetic. In any event, the discovery of indices of predisposition, of whatever origin, should assist in identifying any environmental factors which may act as *precipitating or perpetuating* causes of clinical disorders, and these may well prove to be of primary value in the ultimate control of disease.

DISCUSSION

Dr. J. P. Scott (Bar Harbor, Maine): I should like to congratulate Dr. ...

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mutual fear of human beings and are able to develop close social relationships with them with very little contact It may be concluded that there are genetic differences in dogs in the ability to develop social relations

This raises the question as to whether similar differences occur in human beings Are there individuals who are natively sensitive and timid and who require greater attention in early youth in order to develop proper social relationships? Casual observation would indicate that such emotional differences do exist and I would like to ask Dr Snyder whether he knows of any studies which are being made of genetic differences in the early social and emotional developments of human infants

Dr Snyder I can't think of any at the moment

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CHAPTER II

GENETIC AND ENVIRONMENTAL CONTROL OF ENZYME FORMATION

BERNARD D. DAVIS[1,2]

I should like to expand a point that Dr. Snyder made, that the case of eye pigment is one [illegible] blocked at any one of several reactions [illegible] ave [illegible] e of [illegible] pig-ment formation in those mutants that are blocked before this compound and not in those blocked after it. As Dr. Snyder pointed out, this difference in response among identical pheno-types could have important therapeutic implications.

Recent years have seen the vigorous development of a new field in biology, chemical genetics. This somewhat anomalous hybrid was created when certain biologists broke the rule of biparental inheritance to give rise to an offspring derived from no less than three parents: the *disciplines of* biochemistry, genetics, and microbiology.

I am honored by the invitation to speak for this field here. But I *must* confess that I am also a little disturbed. For it would be wonderful if I could bring you information that would bear directly *on the problem of the* integrated action of the nervous system. But unfortunately, *though a few* abnormal neurological or psychiatric conditions *have been linked to well defined* biochemical disturbances, such as hormonal imbalance [illegible]

[illegible] the opinion, perhaps not shared by all biochemists, that these mechanisms *must long continue to be* studied largely at the psycho-logical and physiological levels of *organization*. For this reason this talk will be limited to a *description of* certain studies on *single-celled* organisms, in the hope of furnishing principles or models that could conceivably apply to your problems. And since *this symposium is concern*- [illegible]

[1] U. S. Public Health Service Tuberculosis Research Laboratory, Cornell University Medical College, New York, N. Y.

[2] The research from our laboratory described in this paper was aided by grants from the Squibb Institute for Medical Research and the Rockefeller Foundation.

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of microbial cells can be grown rapidly, in a small volume, and in a strictly controlled environment—that is to say, in a simple, well-defined culture medium. These factors greatly facilitated the isolation of rare mutant strains as well as subsequent genetic and biochemical studies on them. In addition this approach was based on the unity of biochemistry, and on recognition of the distinction between essential metabolites and essential nutrients. For it had been shown (2, 3, 4) that earlier workers were deceived when they thought that microorganisms with simple nutritional requirements (e.g., a sugar plus some inorganic salts) were particularly simple in their metabolism. On the contrary, such organisms contain as essential metabolites the same variety of amino acids, vitamins and nucleic acid components as those organisms that require these substances as nutrients. The nutritionally simple cells, in contrast to the others, possess the enzymes for making these substances; hence these 'simple' cells are, paradoxically, in a sense the more complex.

Working with a nutritionally simple fungus, the bread mold Neurospora, Beadle and Tatum found it possible to isolate a wide variety of mutants, each deficient in the function of a single essential enzyme, and hence unable to grow unless the medium was supplemented with the product of the blocked reaction. Investigation of these mutants by classical genetic methods combined with chemical procedures for identifying the blocked reaction then disclosed that in this class of nutritionally deficient (auxotrophic) mutants a mutation of a given gene (i.e., a given locus on a chromosome) was invariably associated with a block in a given biosynthetic reaction. These results led to the famous one-gene-one-enzyme hypothesis, which states that the function of each gene is to preside over the synthesis of a single corresponding enzyme. Whether this generalization will extend to all genes is by no means certain, but the generalization has held true, without a demonstrated exception, among the many hundreds of mutants that have been selected for growth factor requirements. A byproduct of this program, and a very large byproduct indeed, was the use of these mutants as marvelous tools for dissecting out previously unknown biosynthetic reactions (5, 6, 7).

Within a few years several workers found that similar mutations could readily be obtained in bacteria, and shortly thereafter Lederberg and Tatum (8–11) discovered that bacteria, long believed to divide only by binary fission, could on occasion undergo a process of genetic recombination akin to sexual reproduction, and hence their genes appear to be located like those of higher organisms on chromosomes. Since bacterial mutants are easier to screen than those of molds and are often more convenient for biochemical purposes, our laboratory has been engaged for some years in biochemical and physiological studies on mutants of *Escherichia coli*, the

factors in controlling patterns of biochemical behavior of individual cells In thus repairing to the lowly single celled organisms we may recall Pasteur's remark that the secret of the infinite will be found in the infinitely small

Now modern biochemistry has become almost synonymous with the study of intermediary metabolism—of the detailed changes that various chemicals undergo in living cells These processes include both degradative reactions, which yield energy and small building blocks and biosynthetic reactions which yield larger building blocks

As a result of such studies two broad principles have emerged The first is that of the specificity of enzyme action—a statement of the fact that each compound is degraded or built up by a series of small stepwise reactions each perfectly comprehensible in terms of organic chemistry and each catalyzed by a specific enzyme And each enzyme has been found in turn to be a particular protein molecule and to catalyze only a single reaction in a single species of molecule or in a group of closely related molecules The second principle is that of the unity of biochemistry—a statement of *the fact that the major metabolic reactions have been found to be identical* in all the organisms studied whether animal plant or microbial Indeed it is striking to observe how much our knowledge of the metabolism of muscle brain or liver cells depends on enzymatic studies on yeast cells left over from beer fermentation It is this principle of unity that encourages us to expect that the more complex aspects of the physiology of microbial cells too can be studied with profit for our understanding of man Let us therefore consider the genetic control of enzyme formation in microorganisms

You are all familiar with the fact that the inheritable properties of living organisms are *under the control of unit factors of inheritance called genes* and that each of these genes ordinarily is reproduced with precision at each cell division Only rarely does a gene undergo a mutation—that is an inheritable alteration While geneticists have generally studied mutations that cause readily visible morphological alterations in rather complex organisms such as the fruit fly or the maize plant it has long been known that inheritable changes could also affect well defined biochemical properties of an organism An example is phenylpyruvic oligophrenia a disease in which the normal path of phenylalanine degradation is blocked because one enzyme of this path is missing As a result phenylpyruvic acid accumulates in the body fluids and for reasons that are not altogether clear certain [illegible] appear

The [illegible] inheritable biochemical lesions was initiated [illegible] (1) A microorganism rather than a higher organism was chosen for these studies because huge populations

SYNTROPHISM

Excretion of Compound X by 83-2, response by 83-1

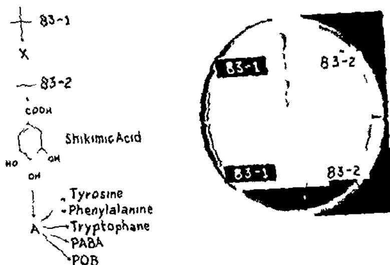


Fig. 1. Cross feeding (syntrophism) involving 5-dehydroshikimic acid (compound X)

this biosynthetic sequence, including both *precursors and* products of shikimic acid and several of these have been *identified as* previously unknown compounds (15) For example figure 1 shows how a mutant blocked immediately before *shikimic acid 83 2*, excretes a compound which can support growth of a mutant *with a still* earlier block 83 1 Hence when these two strains are streaked *adjacent to* each other on a solid medium 83 2 feeds 83 1 The excreted compound was isolated fro... of 83 2 ...

... mutants required still another derivative of shikimic acid *p* hydroxybenzoic acid (POB), which turned out to be a previously unknown bacterial vitamin (*fig. 1*)

There is good evidence that the *shikimic acid* pathway is distributed widely and perhaps universally among pl...

predominant denizen of the mammalian gut. In order to give you a more concrete picture of how these studies are carried out, I should like to describe briefly the steps by which one biosynthetic sequence has been analyzed.

Mutants of a great many types appear spontaneously at a very low frequency in a growing population of *E. coli*, and the frequency can be increased markedly by mutagenic agents such as ultra-violet light or X-rays. But even under optimal conditions of irradiation the total class of auxotrophic mutants reaches only 1 to 2 per cent of the viable population. In order to screen these mutants effectively from their wild-type parents, advantage is taken of an unusual property of penicillin, namely, its ability to sterilize bacterial cells only under conditions that allow growth. In consequence, when a population containing a few mutants is exposed to penicillin in a minimal medium, the wild-type cells grow and hence are sterilized. The various auxotrophic mutant cells, in contrast, cannot grow in a minimal medium and hence survive. They can later be recovered as separate colonies by diluting out the penicillin and incubating on solid media supplemented with a mixture of growth factors—for example, yeast extract. The specific requirement of each mutant strain can then be tracked down by systematic testing with known components of the yeast extract. In this way it is easy to isolate a variety of auxotrophic strains (12, 13).

The use of such mutants to analyze a biosynthetic pathway depends primarily on two facts: a mutant blocked before a given intermediate can in most cases use that compound to satisfy its growth requirement, and a mutant blocked after a given intermediate often accumulates it in the culture medium in large amounts. This accumulation, like that observed in phenylpyruvic oligophrenia, is for the biochemist an extraordinarily favorable consequence of the metabolic derangement caused by the mutation. For normally biosynthetic intermediates are converted in the cell as fast as they are formed, and hence are not present in detectable amounts. Mutants offer an almost unique opportunity to fish these important compounds out of the metabolic stream as they pile up before the dam.

Among the most interesting mutants obtained were a group that required not one compound but a mixture of four: the amino acids tyrosine, phenylalanine, and tryptophan, and the vitamin *p*-aminobenzoic acid. These compounds each possess a benzene ring, and this multiple aromatic requirement was found to be due to a block in a series of precursors of that ring. The first of these precursors to be recognized was a nonaromatic compound, shikimic acid (fig. 1), which was already known as an obscure plant acid. This compound can replace the multiple aromatic requirement of mutants blocked before it, and is accumulated by mutants blocked after it (14). Later, various mutants were found to accumulate other members of

biochemical properties of a cell for example the accessibility of externally added compounds to intracellular enzymes

You can see that the field of chemical genetics has come a long way in the past 12 years since it received such an impetus from the work of Beadle and Tatum And though we are still a very long way from understanding even in the most general terms the biochemical mechanisms underlying the genetic control of such complicated characters as morphology and instinctual behavior an errant gene already has several parameters to play with that we are now able to call biochemical

Before leaving the subject of the genetic control of *enzyme formation* I should like to confess that in the foregoing account there has been a good deal of over simplification For one thing the principle of biosynthesis through a series of successive small steps each on the surface of a different specific enzyme protein appears to apply without question to the formation of small molecules such as the amino acids of which proteins are composed But this principle cannot be extended safely from the amino acids each with a molecular weight of around 100 to the proteins which have molecular weights ranging from tens of thousands to *many millions* An alternative notion has appealed to geneticists and increasingly of late to *biochemists namely* that a complicated macromolecule such as a protein is synthesized on the surface of a single other macromolecule which serves as a template And the one-gene-one-enzyme hypothesis suggests that the gene though probably not itself the template serves as the ultimate source within the cell of the specificity that is transferred via the template to the protein But such speculations have *not yet been successfully translated* into concrete experiments and the mechanism of *protein synthesis* remains the most challenging problem in biochemistry today

The last statement however should be further *generalized* to include not only proteins but all macromolecules that are capable of great variety and hence specificity of structure And in recent years attention has been forcibly drawn to a class of compounds that were hardly given passing mention when most of us went to medical or graduate school the nucleic acids For these substances *have been found* to be just as macromolecular as the proteins and just as capable of being produced by a cell in a tremendous variety of specific configurations One of the most dramatic developments in modern biology *was the demonstration* 12 years ago by Avery MacLeod and McCarthy (99) that a

brought to light a number of metabolic intermediates which are just as important in man as in *E coli* (17 18)

To return from these detailed biochemical reactions to the general problem of gene enzyme relationships we might first look into the question of whether the inability of a mutant cell to perform a given reaction really means that this cell no longer contains the corresponding enzyme or whether the enzyme is present but is inhibited by something in its environment *My colleagues have now investigated this problem by extracting the* enzymes from mutant and wild type cells and measuring their activities under identical conditions including mixtures of the two extracts In all seven mutants studied, each blocked in a different reaction the wild type yielded active enzyme and the mutant yielded none Thus the inferences concerning enzymes that have been drawn from nutritional studies are shown to be generally valid

As a rule it has been convenient for biochemists to work with mutants that have a complete block—i e that are completely unable to grow without the required factor The impression has thereby been created that the effect of a mutation on the corresponding enzyme can only be a complete block in its production But there are many mutants that have incomplete blocks—i e that require a factor for rapid growth but can grow slowly without it Enzymatic studies in the aromatic series have shown that on extraction such mutants yield the enzyme in question but its concentration *is only a fraction of that found in the wild type* (19) It *is* thus clear that mutations can exert quantitative as well as all or none effects on enzyme activity

More important is the finding of my colleague Dr Maas that a mutation *can also lead to the production of a qualitatively changed enzyme* The particular quality chosen for observation was thermal stability because it is easy to screen for mutants with a temperature dependent block One such mutant required pantothenic acid for growth at 37° but grew without *this vitamin just like the wild type at 25° This mutant was* studied in detail and found to contain a remarkably thermolabile pantothenate synthesizing enzyme which is stable in extracts only up to about 20°C (20) Similarly Pauling and coworkers have observed that patients with a hereditary *blood dyscrasia sickle cell anemia have physico chemical* abnormalities in their hemoglobin (21) This substance though not an enzyme is also a protein There is little reason to doubt that qualitative changes of many other kinds can be produced in enzymes as a result of mutation *Indeed biological evolution would be difficult to account for* without such changes

Finally there is evidence that mutations can produce not only quantitative and qualitative changes in enzymes but also changes in still other

factors alone and in some cases environmental factors play only a negligible role in others a very important one To note a familiar analogy, eye color seems to be determined exclusively by genetic factors whereas skin color depends both on one s potential range of pigment formation, which is genetically determined and on one s actual exposure to irradiation

With enzymes the analogous distinction has been made between constitutive ones which are present regardless of the environment in which the cell has grown and adaptive ones which are formed only in the presence of their substrates or of closely related compounds Those enzymes that perform essential functions are naturally constitutive adaptive enzymes are found only among those that perform optional functions An example is the enzyme β galactosidase which splits the sugar, lactose, into components that the cell can utilize as an energy source When cells of the colon bacillus have been grown on lactose they can be shown on extraction to contain plenty of the enzyme while when grown on glucose they contain no detectable amounts of it But on transfer from glucose to lactose they start within a few minutes to form the lactose splitting enzyme And it has been shown that this is a true formation of a new type of protein molecule from amino acids rather than a rearrangement of already existing molecules (26) The genetic potentiality for forming this enzyme exists but its actual formation requires the proper environmental stimulation (27)

This type of adaptation which we might call physiological must be sharply distinguished from genetic or populational adaptation A frequent example of the latter type is that seen when a bacterial strain that is sensitive to a drug becomes more resistant to it on being grown either *in vivo* or *in vitro* in the presence of the drug The two types of a [illegible]

[illegible] change and quite a period of time is required for the progeny of these cells to outgrow the initial sensitive cells in physiological adaptation all the cells respond to the stimulus and the response appears within a few minutes Furthermore genetic adaptation is inheritable persisting indefinitely (except for [illegible]

[illegible] thus lacking the inducing agent

Finally refined methods of analysis have shown that in the process of developing drug resistance the [illegible] spontaneously the role of the [illegible] different from adaptive enzy[illegible] [illegible] in which the substrate has an active inducing role

Genetic adaptation, of course is not limited to drug resistance and both

of more virus particles, the infecting virus particle does not all enter the host cell; only its nucleic acid component does. It thus seems clear that hereditary properties can be laid down chemically in highly specific nucleic acid molecules. And since these molecules, despite their huge size, can pass cell walls, find a functional place in an intact living cell, and then lead to *their own reproduction, the distinction between a gene and a virus is becoming* increasingly hazy. Indeed, one wonders what analogous processes might be occurring in the mammal.

Now these striking advances in our knowledge of the chemical basis of heredity might lead you to expect that the term gene should be taking on an increasingly clear, well defined meaning. The contrary is true. The gene originally received a formal definition as a unit factor of inheritance which controlled some observable property and was distributed among the progeny according to certain numerical laws. These laws implied that the genes were strung as units along a chain-like chromosome which during cell division underwent *frequent random breaks between successive genes.* The cytologist then found that in certain cases he could see these units microscopically, so they became less formal and more material. The physiological or chemical geneticist then defined the gene as a functional unit required for the formation of a given enzyme. But recently it was found that in some cases breaks could occur *within* a functional unit, so the boundaries of a functional unit are no longer congruent with those of a *classical unit. At the same time, as we have seen, in some cases the functional* unit can be identified with a nucleic acid molecule. And two other sources of difficulty should be mentioned. First, though the function of a gene usually does not change when its position in a chromosome is altered, in some cases its function changes considerably with change in position. Second, when the action of a gene has been changed by mutation this effect can sometimes be reversed by another mutation involving a distant gene. *These two effects, of position and of modifier genes, imply that, however* essential a given gene is for the synthesis of a given protein, it is not in absolute and despotic control of that synthesis but is subject to environmental influences. Finally, while most genetic units that have been studied are located on chromosomes in nuclei, a few are located in the cytoplasm (24). The general importance of cytoplasmic factors in inheritance cannot yet be evaluated. You can readily see that the problem of the gene is at *present* in a healthy state of excitement, promise, and confusion (15).

The above account has been concerned only with the genetic factors that control enzyme formation, including both the role of the individual gene and the role of other genetic factors that affect the action of that gene. But the enzymatic *constitution of a cell at a given time is determined by* the interaction of environmental and genetic factors, rather than by genetic

ing further growth the total amount of enzyme in the system remained constant, while the concentration per cell naturally diminished

While this is the usual pattern of adaptive enzyme formation, there is another type which I should particularly like to call to your attention as a possibly useful model for certain aspects of the nervous system That type has been observed only with the production of penicillinase, an enzyme that splits penicillin You will recall the earlier observation that penicillin has the remarkable property of sterilizing bacteria only when they are growing

has observed an analogous phenomenon in the action of penicillin on certain other bacteria which are not sterilized by this drug but rather are stimulated by it to produce the enzyme penicillinase For he found that when penicillin was added to a growing culture the rate of penicillinase production per cell soon became constant, the rate for the whole culture naturally

culture continued to produce penicillinase The rate for the whole culture however, did not increase with growth as it would have done

to develop a penicillinase manufacturing apparatus which then continued like the sorcerer s apprentice to work

persistence of new enzyme producing apparatus appeared to be indefin

Now I would like to take a rash step and express the thought that perhaps this persistent adaptation to penicillinase production might be a useful model for the problem of memory —the problem of

bacterial cell model for this particular problem since its protein metabolism appears to differ fundamentally from that of the mammal For the bacterial cell is built for growth, and present evidence indicates that in a freely growing culture it does not break down any already exist

types of adaptation can be involved in the formation of a given enzyme Thus if we take a strain of bacteria that is unable to split lactose and hence unable to grow on it, and if we plate a million cells or so on a medium in which lactose is the sole carbon source, a few colonies may appear In this process a few cells have first developed by mutation the ability to form, in the presence of the appropriate inducing agent, a lactose-splitting enzyme The lactose in the medium has exerted a double effect it has induced the actual formation of this enzyme in these few cells, and then it has selectively favored their proliferation because it can support their growth but not that of the non mutated remainder of the population, which is genetically incapable of responding to the enzyme inducing effect of lactose

Adaptive enzyme formation may be a more widespread process than has been realized. that is to say, there appears to be an adaptive aspect to the formation of even so called constitutive enzymes, at least in some cases *Thus the substrates of constitutive enzymes are essential metabolites* that can be formed by the cell and are ordinarily present in it at all times, and hence might be exerting an inductive effect on the formation of the corresponding enzymes Such an effect would not be expected to be revealed by changes in the composition of the medium, since such changes would not be expected to prevent formation of the essential substrates However, formation of such substrates can be prevented by mutation affecting an earlier reaction, and we have found that in one such case the enzyme corresponding to the missing substrate was no longer formed in normal amounts unless the substrate was added (29) Others have recently observed a parallel and opposite effect namely, when the end-product of a chain of reactions, an amino acid, is added to a medium in large excess, the formation of enzymes concerned with the synthesis of that amino acid can be completely blocked (30, 31) This adaptive inhibition is indeed an economical device for the cell to employ

The kinetics of adaptive enzyme formation in response to the appropriate stimulus might be worth reviewing briefly, especially in relation to the response of the nervous system to its stimuli The case of the intracellular lactose splitting enzyme has recently been analyzed by Monod and Cohn of the Pasteur Institute (32) They found that in a growing culture the formation of the enzyme began immediately after the addition of the inducing agent, and continued at a fixed rate per cell as long as the inducing agent was present Since the cells were proliferating, this means that in the total culture there was progressive expansion not only of the amount of enzyme, but also if its rate of formation Now as soon as the cells were transferred to a medium that lacked the inducing agent the formation of new enzyme ceased, while the already formed enzyme persisted Thus dur-

with unchanged structure but with changed function: changed as a result of alterations that have arisen either in other genes or in the rest of the cell. Or, alternatively, though there is a one to one correspondence between the chromosomes in a mitotic division, there is a real possibility that during such divisions in a differentiating tissue the individual genetic units on a chromosome may undergo in an orderly manner not only functional, but even structural changes

While on the subject of differentiation, attention might be called to the recent work of Billingham et al (36) These investigators found that foreign skin cells could not be successfully grafted on mice because of the development of an immune response When these cells were injected in an embryo, however, this individual could later, as an adult, accept grafts from the same strain of donors without immune response! It is striking that the cells of the embryo and those of the adult react so differently to the same stimulus

Since we are unable today to analyze the mechanism of differentiation even to the extent of assigning the major role to either the nucleus or the cytoplasm you can see how far we are from having a foothold for biochemical attack It has been disappointing that despite the rapid advance of microbial genetics, there has been no successful microbial model for differentiation, at least none has led to an efflorescence of research such as followed the introduction of auxotrophic mutants as a genetic tool There have been many claims of environmentally directed hereditary changes, especially toward drug resistance, but these have not stood up The closest parallels have involved hereditary cytoplasmic factors, not essential for growth in some cases these could be transferred by infection and hence appear to be viruses, and in other cases, though not obviously [illegible]

and be [illegible]
genetic [illegible]

In addition to the factors that influence enzyme formation, there are others that control the *activity of* the enzymes that are present For it is clear that the cell is not simply a bag of enzymes, even though we sometimes find it convenient for biochemical purposes to pretend temporarily that it is The cell has highly developed [illegible]
it under the most vari[illegible]
exactly the amounts n[illegible]
nisms involved have not yet been extensively analyzed [illegible] however, the mecha-
have already [illegible]
your imm[illegible]

ing protein molecules. In the adult mammal, in contrast, Schoenheimer demonstrated some years ago that in all tissues, including those in which no new cells appear to be formed, the proteins are in a dynamic state (35). This was reported to be true even in the nervous system, although here protein turnover was found to be very slow.

Despite this defect in the analogy, I would still like to pursue it a little further. For memory is undoubtedly associated with persistent material changes in the nervous system, however subtle. If the change involved the production at the time of stimulation of only small readily diffusible molecules, one would hardly expect it to last very long. If the change involved the production, at the time of stimulation, of specific macromolecules, such as those of a particular protein, it would be expected to last longer, but these molecules still might be subject to elimination during the turnover that Schoenheimer described. But if during this turnover the synthetic apparatus of the cell continued to make this postulated macromolecule as it continues to make the other cellular components that are in a steady state of turnover, the level of this substance in the cell would not drop. This is where the model of penicillinase, a persistent, specifically induced new biosynthesis, might conceivably apply.

Finally, I should like to point out that the problem of the persistence of memory parallels another biological problem, that of morphogenesis or embryological differentiation. This is the miraculous process by which genetic material that occupies a volume of about 10 cc. can give rise to the sets of inheritable characteristics of all the two billion human individuals who inhabit the earth. In this process there develop from a single zygote a great variety of cells that differ from each other in their inheritable properties. The process resembles mutation, rather than adaptive enzyme formation, in that the results are inheritable in each cell line. But though the changes are inheritable, the process is unlike mutation, since it is much too orderly to be dependent on chance events; it must involve directive environmental influences on hereditary properties.

Unfortunately we have extraordinarily little insight into the mechanisms involved. It is often stated in biology texts that since the nuclei of various differentiated tissues are all derived from the same zygote nucleus by an uninterrupted series of mitotic division, and since each mitotic division is supposed to result in exact duplication of the chromosomes, then the differences observed between these tissues must depend on heredity-controlling elements in the cytoplasm. But this argument cannot withstand close scrutiny, especially in its implication that each gene must survive differentiation with unchanged function. For since we know that the function of a given gene may be affected by its position or by the presence of other modifier genes, it is quite possible that a gene may survive differentiation

physiological and psychological levels But I wanted to offer a little encouragement for the hope that some day these biochemical models may turn into realities.

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this picture of the present state of the field of chemical genetics and of related areas in cell physiology might be stimulating and even fruitful for you in your research on genetic and environmental influences on the nervous system; and that some years hence, if we should meet again, we will find the gap between our disciplines appreciably narrowed. But despite the extraordinary rate at which research in various aspects of medicine is becoming biochemically oriented, I cannot offer support for the hope—or the threat—that biochemistry will soon 'take over' the study of the nervous system.

DISCUSSION

Dr C Glen King [New York, N Y] First, I want to compliment the speaker on his experimental approach to the work conducted in his own laboratories, and on his excellent presentation of related investigations

It has seemed to me, in evaluating some of the points presented by the speaker, that it is worth while to recognize that we may be approaching a time when the absolute unit of genetics will be a specific formula for a large particle with a molecular weight in the range of several millions At the present time this ideal cannot be reached by scientists, but prospects of such an attainment can readily be envisioned on the basis of techniques and information now available Beyond that point there is little that is absolute in genetics, in view of the evidence that environmental factors are constantly at play, with a risk of altering the structure of molecular units derived from the initial pattern Some units have survival capacity—others do not

Professor George Beadle's group has been developing basic information closely allied with that presented by Dr Davis This new aspect of qualitative and quantitative identification of the respective enzymes that vary with nutritional environment represents both a fundamental and a far reaching phase of genetics and comparative biochemistry

The work by Dr Carl Cori and his associates, in his studies of polysaccharides and monosaccharides as coenzyme fragments, represents another related development of great importance The sugar phosphates were found to serve as specific functional groups attached to the protein particles in enzymes Presumably, such particles are transmitted, preformed or as precursors, in the structure of genes, and in this sense enter into the picture of self propagation

Dr K S Lashley [Orange Park, Florida] I was interested by Dr Davis' suggestion of the similarity between the changes which he described and those involved in learning. Such analogies are, I believe, based upon a misconception of the significance of learning curves Many years ago Robertson compared the curves of learning and forgetting obtained by Ebbinghaus with various curves of chemical reactions He concluded that learning is a reversible,

on the assumption that learning occurs as a single event, that forgetting is always due to interference, as by the postulation of gradual changes Our knowledge of the nature of the learning process is still too limited to justify speculation about it at the level of chemical action

Dr Bernard D Davis (Closing) I would like to thank Dr King for his kind remarks, and in answer to Dr Lashley would like to say, "Amen " I tried to emphasize that I do not consider it profitable to substitute analysis at a superficial chemical le

physiological and psychological levels But I wanted to offer a little encouragement for the hope that some day these biochemical models may turn into realities

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havior in the evolutionary sense, and the identification of physiological and morphological mechanisms controlled by these genes may be expected to expand the horizons of both psychology and physiology.

Many attempts have been made to relate hereditary factors to behavior and to morphological and physiological aberrations involving the nervous system either primarily or secondarily. In the clinical literature this has been done chiefly through the use of pedigree data. In the animal literature genetic interpretations rest on breeding experiments as well. A number of such abnormalities encountered in the laboratory and shown to have a hereditary basis have their striking counterparts in the clinic. Among these are pseudencephaly, encephalocele, spina bifida, syringomyelia, otocephaly, hydrocephalus, spastic spinal paralysis, shaking paralysis, tremors, ataxia, epilepsy, and many others (1). In some of these cases there are frank anatomical concomitants, endocrine deficiencies, or developmental aberrations that can be identified and assigned a causal role. In others there is no known pathological process. Even where lesions exist, the mechanisms by which they develop are not often known. Moreover, where they do exist, the correlations with the symptoms are not always good. For example, although syringomyelia in the rabbit is usually accompanied by pathological changes in the medulla and degeneration of nerve fibers, animals with severe symptoms may be encountered that have only mild lesions, while others may have extensive anatomical damage but show few overt symptoms (2).

Moving to subtler characters, other studies have demonstrated a hereditary basis for temperament. In mice, for example, it has been shown that there are differences in aggressiveness as measured by readiness and ability to fight among highly inbred strains. The ratings for the same strains are different in the studies here cited (3, 4), but the reasons for the differences have been identified. In the work of Ginsburg and Allee, ratings were based on performance after considerable fighting experience, i.e., on the ability of an animal to develop a pattern of responses after long experience. Scott, on the other hand, based his ratings on the pre-fighting aggressive manifestations elicited from relatively naive mice. By either set of criteria, reliable and repeatable strain differences may be obtained which, when considered together, characterize these animals both with respect to naive performance and reaction to specified experiences. An extensive literature has since developed on the subject, in which psychological and physiological factors have also been studied and evaluated along with the genetic findings (5, 6, 7). Had the latter not been available, stereotyped strain responses could have been erroneously referred to elements of an experimental design. This is especially likely in behavior studies with animals that are genetically distinct by virtue of belonging to small labora-

tory colonies inbred over a period of some ten or a dozen generations These are then designated as albino mice or hooded rats and compared with albino mice or hooded rats from other colonies that may have little in common with them genetically so far as the attributes under investigation are concerned Since various aspects of behavioral potentialities ranging from maze learning ability to aspects of temperament are affected by the genetic constitution of the animal and since these genetic effects have been demonstrated with precisely those forms most commonly used in behavior studies the uncontrolled genetic variable may well be a major source of error where it has not been explicitly considered (8, 9, 10) In a small or moderate sized animal colony that has not been rigorously inbred or subjected to the strictest selection with respect to the trait in question, the use of littermates does not constitute an adequate genetic control If there is an appreciable heterozygosity for genetic factors affecting the experimental outcome these will segregate among littermates making

... than to use the split litter technique where, whatever the number of litters or animals involved in the latter procedure, they trace back to a limited number of relatively recent matings within the colony

In the light of the growing evidence that behavioral traits ranging from frank abnormalities to subtle shadings of temperament and maze performance demonstrably have a genetic basis in a number of commonly used laboratory animals (1 5 8 9 10 11 12) and that these have only in a relatively few cases been demonstrably due to a particular anatomical or physiological factor we thought it of some importance to investigate a complex genetically controlled behavior reaction in detail The objectives of this research are to analyze the *genetic basis* for a given syndrome as completely as possible and to study the *intervening* variables that lead to the ultimate behavioral effects

The character chosen for study was susceptibility to sound induced seizures This occurs on a genetic basis in deer mice (13 14), house mice (15 16 17) rabbits (1 18 30) and rats (19 20) Early reports on the rat attributed seizure susceptibility to a single ...

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In ... ouse mouse (*Mus musculus*) seizure susceptibility is widespread It occurs in a number of inbred strains (15, 16 21) and there is a variety

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Many attempts have been made to relate hereditary factors to behavior and to morphological and physiological aberrations involving the nervous system either primarily or secondarily. In the clinical literature, this has been done chiefly through the use of pedigree data. In the animal literature genetic interpretations rest on breeding experiments as well. A number of such abnormalities encountered in the laboratory and shown to have a hereditary basis have their striking counterparts in the clinic. Among these are pseudencephaly, encephalocele, spina bifida, syringomyelia, otocephaly, hydrocephalus, spastic spinal paralysis, shaking paralysis, tremors, ataxia, epilepsy, and many others (1). In some of these cases there are frank anatomical concomitants, endocrine deficiencies, or developmental aberrations that can be identified and assigned a causal role. In others, there is no known pathological process. Even where lesions exist, the mechanisms by which they develop are not often known. Moreover, where they do exist, the correlations with the symptoms are not always good. For example, *although syringomyelia in the rabbit is usually accompanied* by pathological changes in the medulla and degeneration of nerve fibers, animals with severe symptoms may be encountered that have only mild lesions, while others may have extensive anatomical damage but show few overt symptoms (2).

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in addition, been available in a variety of breeds or lines with some considerable inbreeding hereditary proneness to convulsive behavior has been noted. One would therefore predict that, with comparable study and analogous breeding programs, the same situation could obtain in other forms as well.

One question that invariably arises with respect to these researches is their bearing on the seemingly allied problem of human epilepsy. Some workers have, in their terminology, implied that these seizures are epileptiform. Others have carefully avoided the analogy. Since this is a problem of both theoretical and practical importance, a judicious begging of the question, though scientifically impeccable, is to be avoided in favor of a less prudent evaluation of the possible bases for such an analogy. In terms of overt behavior the comparisons can certainly be made. However it may be argued that the dependence of the animal convulsions on sound, points to the involvement of the middle or inner ear, and that, should this view of the etiology of the seizures prove erroneous, their dependence on sound is still a serious point of difference.

That this is not a matter of ear abnormality has been demonstrated (28, 29). Moreover, the animal seizures may be spontaneous (30) or may be elicited by factors other than sound (31, 32). Conversely, clinical epilepsy may be sound induced (33). A more conclusive relationship between audiogenic seizures in animals and human epilepsy has recently been established by the fact that 2-acetylamino-1, 3, 4-thiadiazole-5-sulfonamide, a substance reported to be effective in the treatment of clinical epilepsy, is also effective in preventing or ameliorating seizures in genetically susceptible mice, rats, and rabbits, where these are sound induced, but is less effective against convulsions produced by electroshock or metrazol (34).

One more consideration remains before the details of our experiments are presented. This has to do with the means by which the hereditary basis for seizure susceptibility is established. As has been pointed out, seizure incidence is a function of the experimental situation. Depending on age (21), amount of prestimulation (35, 36), schedule on which repeated trials are run, nutritional condition (runts are more resistant than their normal littermates, but specific dietary deficiencies 37, 38, 39 increase seizure incidence) and the characteristics of the sound stimulus, one or another convulsive incidence may be obtained with a given inbred strain. The particular incidence reported is in this sense an artifact, and it is this artifact that is taken as the starting point for genetic analyses. The answer, of course, is standardization in the interests of consistent and repeatable results, but standardization ...

to

of genes involved The seizure characteristics of a given strain in a particular experimental situation is easily delineated in terms of age of maximum susceptibility latency incidence seizure profile type of recovery and effects of prestimulation The strains worked with most extensively thus far differ with respect to the inherited basis for seizure susceptibility (16 17) In fact closely similar seizure characteristics have been observed where the genetic basis for susceptibility is demonstrably different In such cases there is evidence that *the intervening physiology is different too* and that palliative agents that are effective in the one case may not be effective in another that is phenotypically similar but genetically distinct (22 23)

Illustrations of the fact that inherited seizure susceptibility may be widespread in *Mus musculus* are provided by two recent developments each of which has given new impetus to research in this area The inbred strains tested by Fuller, Ginsburg Hall Miller Roberts Ross Vicari and others *were all developed at the Jackson Laboratory primarily for cancer* research and allied studies In 1946 Hall (15) tested representatives of some of these strains at random and found that in the complete absence of selection for this trait the strains differed widely in susceptibility to audiogenic seizures This finding gave rise to the work by the investigators just mentioned

A completely different line of approach was used by the Frings (24) They began selecting for seizure susceptibility in a population of mongrel albino mice Not only were they able to achieve the desired results but they were also able to produce lines that differed widely from each other in their seizure patterns

It is clear that the diverse populations from which the many strains at the Jackson Laboratory were derived carried an appreciable number and variety of seizure genes that came to be differentially represented in the various inbred strains as these were developed in the total absence of *selection for or against convulsive behavior In a wholly different and* relatively small population chosen at random by the Frings such genes were again present

As has already been mentioned they are also found in deer mice (*Peromyscus*) rabbits and rats Since these forms are taxonomically allied it may be well to ask whether *seizure genes are also found in other mammalian* or vertebrate groups Localized tremors on an inherited basis have been reported for dogs (25) as have cases of recurrent tetany (26) and epilepsy (27) In addition running fits attributed to sound have been casually noted

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studied from both the behavioral and the genetic point of view and have

TABLE 1

Substances reducing seizures and/or fatalities in DBA/1 mice

Substance	Dose	Sex	No.	Major effects	Probability*
	mg/10 g				
Alanine 30–45 min	30	M+F	70	Deaths/cons −15%	003
Diamox 2³₄ 3 hrs	5	M+F	67	No cons., no deaths	< 0000000000[illegible]
Dinitrophenol 30–45 min	15	M+F	70	Deaths −11 4%	016
γ glutamylhydrazide 30–45 min	2	F	35	Cons −16 6% Deaths −18 2%	03
		M	34	No effect	
Glutamic acid 30–45 min	20	M+F	132	Deaths & cons −43%	< 00000000002
Glutamic acid 72 hr re-test	20	F	31	Cons "normal" Deaths −21 7%	0000005
		M	34	Deaths, cons "normal" Deaths/cons −15%	028
Lactic acid 30–45 min 3d day	21 (daily—3d)	M+F	46	Cons −50% No deaths	00000002
Oxaloacetic acid 30–45 min	25	M+F	70	Deaths/cons −24%	000063
Succinic acid 30–45 min 3d day	20 (daily—3d)	M+F	2[illegible]	Cons −50% Deaths −43%	00003

* Calculated for the difference of greatest magnitude

direction from the expected incidence have an approximately equal chance of occurring and being detected

Table 1 lists those substances that reduce seizures and/or increase recoveries It should be noted that they do not produce anaesthetic or other overt effects at the doses used.

at the same time, putting each at some point on a scale of convulsive behavior where its characteristics can be measured.

MATERIALS AND METHODS

Four highly inbred strains of mice were used in the accompanying studies. These were DBA/1, DBA/2, C57/C and C57/10. The first has an intermediate susceptibility under our experimental conditions and was selected as the "standard" strain for screening substances having presumptive effects on seizures, since either enhancement or suppression could be easily detected. The second has a high convulsive risk, and the last two have a low seizure risk and are behaviorally indistinguishable from each other by our methods. When the latter are used in identical crosses and their progeny compared, the phenotypically identical parent strains are seen to be genotypically different.

All mice were tested at 30-35 days *post partum* by exposing them individually for 1½-2 minutes to a doorbell suspended above a galvanized iron washtub 60 inches in circumference at the bottom. Tests with a sound meter showed an average sound pressure of 95 ± 1 decibels. Behavior records were taken during each test and the times of onset of rapid running, convulsion, and recovery or death were recorded, using a stopwatch. Seizures were classified in order of severity as clonic, tonic-clonic and convulsive spasms (40).

Where substances were screened for effects on seizures, doses were determined either from the literature or by direct tests. The desired dose was one that just fell short of producing overt symptoms in any animal, i.e., a maximal non-toxic dose. The interval between injection and testing was determined from the lowest toxic dose; that is, animals receiving the desired quantity of a compound were tested after an interval corresponding to that in which toxic symptoms were observed on a slightly higher dose of the same compound. All injections were subcutaneous unless otherwise indicated. Acids were neutralized with sodium hydroxide and brought to pH 7.0-7.4.

RESULTS

Genetics.—The results of genetic experiments have been reported elsewhere (15, 16, 17). These are still in progress in our laboratory. They indicate that the basis for susceptibility in these strains is genetically complex and that each is genotypically distinct from the other. One point may be singled out for special mention here. It is that the results of reciprocal crosses differ, but in a manner that does not suggest either sex linkage or some simple involvement of the Y chromosome. The assumption that there are maternal effects that vary with the strain is also inadequate, although this has not been ruled out as a contributory factor and can, moreover, be tested directly using ova transplants and foster nursing. In the light of other experiments, especially those involving glutamic acid and related substances (41), it seems more probable that the sex differences are related to the genetic background through intervening effects on endocrine balance.

Screening of metabolically active substrates. Tables 1 to 4 summarize the effects obtained by Ginsburg and Roberts (22, 23) as a result of screening a number of metabolically active substrates and antimetabolites, especially in the DBA/1 strain, which has an intermediate incidence under our experimental conditions so that, in a formal sense at least, deviations in either

TABLE 3

Substances having no effects on seizures or fatalities in DBA/1 mice

Substance	Dose	Sex	No	Sex difference	Probability
	mg/10 g				
Untreated		M F	776 667	M 11 1% more conv 11 5% more deaths	00006
Aspartic acid 30–45 min 3 1 day	6 25 (daily—3d)	M+F	35	None	
Dextrose 30–45 min 3 1 day	10 (daily—3d)	M+F	40	None	
Fumaric acid 30–45 min	5	M+F	70	None	
γ aminobutyric acid 30–45 min	10	M+F	66	None	
Methionine sulfoximine 4½ hrs	8	M+F	48	None	
0 9% saline 30–45 min	9	M F	125 134	M 15 1% more conv 13 2% more deaths	014

tem Roberts (22, 23) has attempted to follow the fate of most of these substances using paper chromatography, but with only partial success During the seizures the permeability relations in the vascular beds are also altered (42) so that normal inferences regarding the so-called blood brain barrier no longer hold A partial rationale for some of the effects reported here has been attempted previously (41, 43)

Three definite findings especially pertinent to our major topic emerge

1 The effects of glutamic acid are counteracted by substances known to be metabolic antagonists when studied in bacterial systems (44), suggesting that in the present case as well, the effect is at an enzymatic level

2 The exaggeration of the normal sex difference occurs only with glutamic acid glutamine and their antagonists Other substances having effects of equal magnitude and direction do not act differently in the two sexes

3 Diamox (2 acetylamino 1 3 4 thiadiazole 5 sulfonamide) a potent [illegible]

[illegible] a suggestive evidence that this is correlated with the state of acidosis or alkalosis at the time

At present we have no rationale with which to explain the mode of action of these substances on any common basis. A comparison with substances that enhance seizures (table 2) or with those that have no effect (table 3) complicates the situation still further, since, for almost every hypothesis adequate to account for the actions of a number of compounds that reduce seizure susceptibility (table 1), there is a contradiction in table 2 or 3.

The picture is further complicated by the fact that many of these substrates are easily interconvertible, and the procedure of injecting a particular one into the intact animal does not insure that it remains in that form or that a significant amount accumulates in the central nervous sys-

TABLE 2

Substances increasing seizures and/or fatalities in DBA/1 mice

Substance	Dose	Sex	No	Major effects	Probability*
	mg/10 g				
α ketoglutaric acid 30–45 min 3d day	20 (daily—3d)	M+F	32	Conv +36 3% Deaths +33 8%	00009
α methylglutamic acid 30–45 min	50	M+F	70	Conv +32 6% Deaths +19 9%	0000005
				M deaths 20 8% over F	012
Diamox 48 hr retest	5	M+F	37	Conv +40 3% Deaths +42 0%	00005
γ glutamylhydrazide 30–45 min	3	M	35	Conv +26 6% Deaths +27 4%	00022
		F	35	No effect	
Glutamine 30–45 min	20	M	35	Conv +32 9% Deaths +21 7%	00015
		F	35	No effect	
Malic acid 30–45 min	22	M+F	70	Conv +40% Deaths +34 3%	000000002
Methionine sulfoxide 30–45 min	50	M+F	60	Conv +32 3% Deaths +12 8%	0000006
Pyruvic acid 30–45 min 3d day	25 (daily—3d)	M+F	29	Conv +35 4% Deaths +32 2%	0002
Sodium bicarbonate 30–45 min 3d day	19 (daily—3d)	M+F	50	Conv +19 7%	007

* Calculated for the difference of greatest magnitude

the seizure incidence by 25%. The circumstance that the convulsions were not increased in C57/6 mice by agents which increased them in the DBA/1 strain cannot, therefore, be explained away by the assumption that the former are absolutely refractory.

In a previous paper (41) it was found that repeated daily injections of glutamic acid into DBA/1 mice did not alter the convulsing characteristics of the females, and did not lower the incidence in males although it did reduce the proportion of fatalities in that sex. Table 1 shows that a single injection of glutamic acid lowers the seizure incidence profoundly in both sexes, thereby indicating that adaptation occurs upon repeated administration and that it is more complete in females than in males. In the work on repeated administration the fatalities were reduced in two ways. In the first place, there was a higher proportion of milder seizures among males, and these do not ordinarily terminate fatally. Over and above this, there was a significant reduction in fatalities that are ordinarily expected as a result of clonic-tonic seizures. Such animals can be resuscitated using art fic al r ... r

... respiratory center during the period of anoxia which it could not otherwise withstand (35, 41).

A further sex difference in the action of glutamic acid is revealed by the work of Ginsburg and Fuller (35). Here glutamic acid pretreatment was compared with a pattern of interrupted stimulation that also reduced the convulsive risk in DBA/1 mice. Interrupted stimulation affected the two sexes identically and recoveries were increased solely as a result of the decreased severity of the convulsions. Glutamic acid lowered the seizure incidence and increased recoveries from convulsions in both ... greater ...

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that a much higher control incidence was obtained, so that, with a commensurate percentage reduction in seizures, the difference in males and females could be expressed. In the studies summarized in the tables, the

In our laboratory this evidence has been of two kinds First, that the protective effect is not obtained during the initial half hour following the subcutaneous injection of Diamox and becomes maximal only after an interval of some three hours Second, that both the protective effect and the later aggravation of the seizures observed with Diamox can be duplicated with ammonium chloride

Diamox also appears to be acting via a different mechanism than glutamic acid Whereas the former protects all strains of mice we have tested and has, in our hands, analogous effects upon seizure prone rabbits, the latter does not act with equal effectiveness in these forms (table 4) Nor was α methylglutamic acid effective in increasing seizures in the resistant C57/6 strain Three other substances (malic acid, pyruvic acid, and α keto glutaric acid) that increased seizures in DBA/1 mice were also tested in C57/6 mice with no effect

The fact that seizures can be increased in these (C57/6) mice has been demonstrated by using a prodding device that forces the mice to run, rather than remain immobile, during the latent period In our hands, this increased

TABLE 4

Effects of metabolically active substrates on DBA/2 and H S mice

Substance	Dose	Strain	Sex	No	Major effects	Probability*
	mg /10 g					
Untreated		DBA/2	M F	100 100		
Untreated		H S Frings	M+F	327†		
Glutamic acid 30–45 min	20	DBA/2	M F	35 35	Conv −32 7% Deaths −62 2% M conv 20% over F	< 000000000002 008
Glutamic acid 30–45 min	20	H S	M+F	72†	No effect	
Diamox 2^{3}_{4} 3 hrs	5	DBA/2	M+F	69	Conv −96 6% No deaths	< 000000000002
Diamox 2^{3}_{4} 3 hrs	5	H S	M+F	72†	Conv −66 7% No deaths	01

* Calculated for the difference of greatest magnitude

† Animals X trials

this is magnified by glutamic acid glutamine, and their antagonists but not by other oxidizable substrates having similar effects in magnitude and direction suggests that the glutamic glutamine axis is more closely associated with the fundamental aberration than are the other effective agents that to date have not been experimentally related to the sex difference. The fact that there is a sex difference at weaning age and that substances normally metabolically available to the animal can magnify it when present in large excess poses an entirely new physiological problem as does the phenomenon of adaptation to repeated doses of glutamic acid where again the sex difference occurs as early as two to four weeks of age.

It is interesting that those substances affecting the seizures in DBA/1 mice are related to biochemical mechanisms controlling energy release, and on this basis it is suggested that the biochemical mechanisms concerned with energy release in the nervous system may be under genetic control and have an important relationship to behavioral abnormalities. This notion would carry still more weight if as in the case of glutamic acid metabolic antagonists of some of the other agents would reverse their effects on the seizures.

It has been pointed out that sonogenic convulsions in rats are enhanced by particular dietary deficiencies (37 38 39 45) and that in every established cas

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If therefo ... hypothesis is correct deficiencies in particular reactions leading to normal controlled energy release in the nervous system whether these are due to genes or to dietary deprivation of necessary co-factors are the basis for the seizures.

The problem of whether or not these studies have any relevance for human convulsive behavior has already been touched upon. Seizures tremors etc are common in mammals and have a demonstrable genetic basis in many instances (13 14 15 16 17 18 19 20 25 26 27). As was mentioned in the introduction many other nervous system abnormalities analogous to those encountered clinically are frequently found in lower animals especially where there has been considerable inbreeding occurring independently in relatively unrelated stocks in a number of laboratories. Since many of the traits involve recessive genes that occur with a low or moderate frequency in the population as a whole they would reach infrequent phenotypic expression under conditions of random mating and the occasionally afflicted individual's immediate ancestors would not have exhibited the character which they nevertheless transmitted. When such genes occur in a laboratory colony they are spread around the colony as their carriers produce litters and with continued interbreeding of these

reduction was from a lower initial base, and the values after treatment were so low that the sex difference could have been masked.

DISCUSSION

The data presented could be discussed from a number of different points of view. Although we are primarily interested in the mechanisms by which genes determine seizure susceptibility and resistance, this is not the point to be emphasized here considering the present state of our knowledge. Rather it is that a given behavioral entity can be due to a variety of distinct causes. The C57/6 and C57/10 mice are, as has been mentioned, behaviorally indistinguishable with respect to this trait but the genetic basis for the common behavioral phenotype is different for each as determined by breeding experiments. It is conceivable that more refined techniques might distinguish them phenotypically as well, as is the case with DBA/1 and DBA/2. These are or are not alike with respect to seizure incidence depending upon the quantity of prestimulation that is encountered in the testing procedure (35, 36). The importance of distinguishing similar or identical phenotypes genetically where such a distinction exists is that the various genotypes may not respond similarly to identical treatment and that this is true because some of the intervening physiological variables are different.

As was mentioned in the preceding section Diamox acts similarly in three genetically distinct seizure susceptible populations of mice and in epileptic rabbits while glutamic acid on the other hand does not. Nor is α methylglutamic acid, a structural analogue and metabolic competitor of glutamic acid, capable of increasing seizures in C57/6 mice at doses that produced this effect in DBA/1 animals despite the fact that the former are capable of exhibiting much higher seizure rates under other experimental conditions. Glutamic acid is not a general anticonvulsant any more than α methylglutamic acid is a general convulsing agent although each can be considered to have the effect mentioned with respect to a particular inbred strain and can be used within determinable margins of error to distinguish one genotype from another.

So far as therapeutic uses are concerned, substances having a uniform effect on all genotypes within a phenotype have an obvious practical value. From a research point of view, the others are more interesting. The discovery, for example, that the action of glutamic acid in a given strain can be reversed by metabolic competitors that are structural analogues and that other strains do not react in the same way to these substances suggests that the gene determined aberration has a metabolic basis for which glutamic acid can, in part, compensate. The finding that there is a small but reliable sex difference in untreated DBA/1 mice at weaning age and that

are not apparent where mere overt behavior is taken as the basis for erecting experimental or clinical categories. Since it is usually either impracticable or impossible to secure adequate genetic information to permit classification by genotype, especially in clinical studies, advantage should be taken of the fact that the underlying physiological mechanisms are under genetic control and thus correlated with the genotype, and illustrations are given in which it is possible to conduct diagnostic tests that permit one to subdivide a given behavioral category on this basis.

In view of the foregoing, it is suggested that the gene controlled behavior reaction is the 'natural' unit for investigation, and data are cited to demonstrate that environmental agencies produce effects similar to, if not identical with known genetic abnormalities.

The gene controlled behavior reaction is also examined as an evolutionary unit and the problem of extrapolation from simple to more complex organisms, and especially from experimental studies on higher mammals to clinical studies in man, is discussed in the light of particular instances and related to the problem of therapy.

DISCUSSION

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carriers and their progeny, they come to more and more *frequent expression*. The fact that a given human pedigree behind an abnormal individual shows no similar abnormality does not, then, eliminate a hereditary basis for the trait. Nor does the circumstance that the abnormal behavior may be precipitated by some environmental agency eliminate hereditary factors as is demonstrated by the sound induced seizures here reported.

In perusing the literature that has most immediate relevance to our problem we have come across a number of instances where the lack of *adequate genetic controls have negated* a good deal of experimental work. We are convinced that this has been the case with a number of discrepancies in the clinical and animal literature regarding the efficiency of such agents as glutamic acid as anti-convulsants and as aids to learning. These instances have been reviewed in another paper (41).

Finally, it is our *opinion that where the syndrome in question rests* upon morphological or physiological derangements in elements that man has in common with his primate, mammalian or vertebrate ancestors, *there is no reason to suppose that similar genetic physiological and developmental* factors are not involved. The trait may be modified in its expression because of man's infinitely more complex nervous system and behavioral repertoire but may *still have essential* elements in common with its counterpart in lower forms.

SUMMARY

Data are presented which demonstrate that genes affect behavioral capacities in a number of ways that can be specified in detail and related to morphological, developmental or physiological concomitants. Particular attention is paid to the metabolic events that control energy release and to evidence that these *metabolic mechanisms* are under genic control and that the genetic capacities of the nervous system, metabolically speaking, have known behavioral sequelae which can be either exacerbated or controlled by known *enzyme inhibitors and/or metabolic intermediates*. Instances are cited of superficially identical behavioral abnormalities that are genetically distinct, and evidence is given to demonstrate that the underlying physiological causes are also distinct and are *correlated with* the genotype rather than the phenotype. Contradictions in the literature of animal psychology and in clinical reports are investigated from this point of view and shown experimentally to be due to the fact that the behavioral phenotype was used as the basis for diagnosis or classification in instances where it could be demonstrated that the unitary behavioral class consisted of several different genotypes and that each of the latter had its own distinct physiology. It is therefore suggested that both experimentation and therapy must take account of genetic variables that

are not apparent where mere overt behavior is taken as the basis for erecting experimental or clinical categories Since it is usually either impracticable or impossible to secure adequate genetic information to permit classification by genotype, especially in clinical studies, advantage should be taken of the fact that the underlying physiological mechanisms are under genetic control and thus correlated with the genotype, and illustrations are given in which it is possible to conduct diagnostic tests that permit one to subdivide a given behavioral category on this basis

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DISCUSSION

Dr K S Lashley (Orange Park Florida) This study of Dr Ginsburg is the most thorough

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When the physiology of a behavior trait is analyzed it is seen that there are several places where the genes might possibly act As Dr Lashley points out, genes could modify the anatomy and physiology of the sense organs, the physiology of motor processes in either the voluntary or involuntary muscles and finally, they could affect the physiology and biochemistry of the nervous system itself

This work of Dr Ginsburg is particularly interesting in that it shows that there is at least a possibility that hereditary factors may act directly upon the central nervous system through its metabolism If this is true it would appear that if a factor has a general effect on nervous metabolism the final effect on behavior is general and disrupting This is logically what might be expected but I wonder if there is any evidence of general biochemical defects which produce milder effects?

DR BENSON F GINSBURG (Closing) In answer to Dr Scott's question there are biochemical defects that produce milder effects I am persuaded that when such defects have been extensively studied the milder ones will be found to predominate They are however more difficult to detect and harder to study The advantages of working with an extreme trait such as the one just reported are that it is unmistakable and that when it has been modified experimentally this too is unequivocal The physiological concomitants are so severe that it is difficult for them to escape detection The tremendous contrast between the abnormal trait and the normal also simplifies the genetic analysis As Dr Snyder mentioned earlier the same situation obtains in the clinic where the extreme and spectacular cases are the first to attract attention and to stimulate investigation In due time the milder aberrations may be expected to come in for their share of attention and I am confident that this will be the case here

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CHAPTER IV

GENETIC FACTORS AFFECTING SUSCEPTIBILITY AND RESISTANCE TO VIRUS DISEASES OF THE NERVOUS SYSTEM

ALBERT B. SABIN[1]

INTRODUCTION

Most viruses which attack the nervous system of human beings and animals produce recognizable disease in only a small proportion of infected individuals. It has been established beyond doubt by means of specific tests for antibody that the vast majority of human beings infected with the viruses of poliomyelitis or of the various types of encephalitis exhibit no recognizable signs of involvement of the nervous system. Many factors, some pertaining to the viruses and others to the infected hosts, have been shown to influence susceptibility and resistance. Determination of the role of any one factor is difficult except under carefully controlled experimental conditions. The studies of Lynch and Hughes (1) with the virus of yellow fever and those of Webster (2, 3) with the viruses of louping ill and St. Louis encephalitis in mice provided the first experimental evidence that the genetic constitution of the host can determine the outcome of mammalian viral infections. However, the strains of virus used by these investigators did not permit a clear-cut analysis of the mechanism of genetic resistance, because no uniformly resistant animals were available and the cause for the lack of uniformity had not been elucidated. The accidental discovery that the mice which had been bred for many years at the Rockefeller Institute at Princeton (hence called PRI) were uniformly resistant to the 17 D strain of yellow fever virus has permitted a genetic and virologic analysis of some of the factors underlying inherited resistance to infection (4).

EXPERIMENTAL STUDIES

Genetic mechanism of inheritance of resistance

Swiss mice inoculated intracerebrally with the 17 D strain of yellow fever virus develop paralysis of the extremities and invariably die. As little as 1/100 000 to 1/1 000 000 ml. of 10 per cent extract of infected mouse brain

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and cord can produce this effect In the 1 to 2 month old mice used in this study, this fatal infection is associated with minimal or negligible lesions in the nervous system, the clinical manifestations resulting from interference with neuronal function rather than destruction of the cells PRI mice, inoculated intracerebrally with the largest to the smallest amounts of this virus, become infected as is evident from development of antibody, but exhibit neither clinical nor histologic evidence of the infection The genetic mechanism of inheritance of this spontaneous resistance was investigated by cross breeding experiments, in which the progeny were tested by intracerebral inoculation of approximately 10,000 LD_{50} of this virus and the appearance of clinical manifestations and death were recorded

The results summarized in figure 2 indicate the following

a) F_1 progeny 100 per cent resistant
b) F_2 progeny 72 per cent resistant
c) Backcross of F_1 to susceptible (Swiss) 50 per cent resistant
d) Backcross of F_1 to resistant (PRI) 100 per cent resistant
e) F_2 susceptibles crossed with susceptibles (Swiss) 100 per cent susceptible
f) F_2 resistants crossed with susceptibles (Swiss) yielded 2 types of litters some with 100 per cent resistant and others with 54 per cent susceptible
g) Backcross resistant progeny resulting from (F_1 × Swiss) crossed with susceptibles (Swiss) 57 per cent susceptible

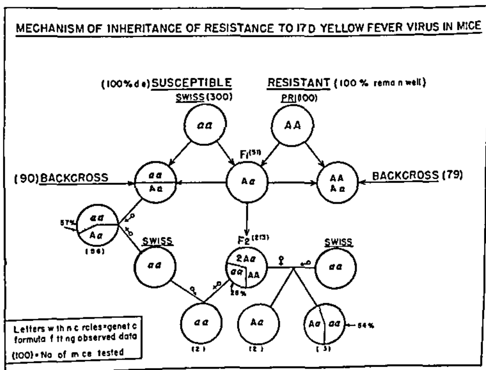


Fig 2

While these data are in accord with the Mendelian laws for a single pair of autosomal genes it is difficult to rule out other possibilities involving multiple linked genes with a very low percentage of crossing over

Viral multiplication in genetically resistant host

Tests for the level of viral multiplication in the brains of PRI and Swiss mice sacrificed at different intervals after intracerebral inoculation revealed that the virus multiplied in the genetically resistant mice but at a level only $^{1}/_{10\,000}$ to $^{1}/_{100\,000}$ of that achieved in the susceptible mice It was evident therefore that the genetic factor operated by depressing the level of viral multiplication The progeny which segregated out of the various crossings were phenotypically like the parent resistant or susceptible stocks i e the resistant ones not only failed to die but also showed no clinical signs of disease while the susceptible ones showed the same incubation period and high level of viral multiplication as the Swiss mice Although the yellow fever virus does not multiply to as high a level in the testis as in the brain of Swiss mice, it was found that the virus also multiplied at a lower level in the testis of the genetically resistant PRI mice It may be of interest to note here that cortisone had no effect either on the level of viral multiplication or on the outcome of the infection in the genetically resistant mice

Selective action of multiplication-depressing factor on various viruses proliferating in mouse brain

The genetic factor in PRI mice which depresses multiplication of the yellow fever virus was found to have a similar effect on the viruses of dengue fever West Nile fever Japanese B St Louis and Russian spring summer encephalitis which are also linked together by a chain of common antigens and other properties (5) but it was without effect on a large number of other unrelated viruses listed in table 5

Localization of genetic factor in the cells affected by the virus

Webster and Joh[illegible]

to multipl[illegible]

resistant n[illegible] brain tissue of susceptible mice

The experiment summarized in table 6 and reported here through the courtesy of Dr Alice E Moore indicates that virus multiplication is not depressed in foreign tumor cells which grow in the genetically resistant host while it is depressed in the brain tissue of the same host This strongly suggests that the genetic multiplication-depressing factor is not produced in the host outside the cells in which the virus multiplies

TABLE 5

Selective action of multiplication depressing factor of PRI mice on various viruses proliferating in mouse brain

Action	Virus
Multiplication depressed PRI mice completely or partly resistant	Yellow fever Dengue fever West Nile fever Japanese B encephalitis St Louis encephalitis Russian Spring Summer encephalitis
Multiplication not affected PRI mice fully susceptible	Western equine encephalitis Eastern equine encephalitis Venezuelan equine encephalitis Poliomyelitis Mouse encephalomyelitis— TO ' Rabies Lymphocytic choriomeningitis Herpes simplex Vesicular stomatitis Rift Valley fever Sandfly fever

TABLE 6

Experiment showing that inhibition of virus multiplication is a function of the cells of the genetically resistant host and does not occur in foreign implanted cells

Sarcoma 180 implanted in PRI' and Swiss' mice—grew equally well in both 6 days later Russian encephalitis virus injected into tumors Mice sacrificed at indicated intervals and virus titered in brain and tumor

Virus in	Swiss mice			PRI mice		
	1 day	4 days	7 days	1 day	4 days	7 days
Tumor	4.5*	8.5	6.5	5.5	8.0	8.0
Brain	2.5	4.0	8.5	0	4.5	4.0
Clinical result	Mice died of encephalitis			Mice survived		

* Reciprocal of log of LD_{50} The data shown in this table were obtained by Dr Alice E Moore

Role of special cellular vulnerability at low levels of viral multiplication in abolishing resistance based on genetic multiplication depressing factor

During the course of this work it was discovered that the cells of new born or older immature mice (depending on the virus) may be more vulnerable

TABLE 7

High cellular vulnerability at low levels of viral multiplication as a factor in susceptibility

Strain of yellow fever virus injected intracerebrally	Mice		CNS signs and death	Level of virus multiplication peak titers per p… rocal log LD50
	Strain	Age		
17 D	Swiss	3 weeks	+	7 5
	PRI	3 weeks	0	1 8 3 3
	PRI	4 days	+	2 5 3 7
French neurotropic	Swiss	3 weeks	+	7 0 8 2
	PRI	3 weeks	76% 0	4 2 4 4
	PRI	3 weeks	24% +	3 2 3 8

TABLE 8

Experiment showing that inherited virus multiplication-depressing factor may not impart resistance until animal has reached age of maturity

St Louis Encephalitis Virus (Webster No 3)

Injected intracerebrally

Weight (age) of mice	PRI resistant	Swiss susceptible
gm		
8	7/10	10/10
12 14	9/20	10/10
20 25	0/20	10/10
31 36	0/10	10/10

at low levels of viral multiplication, and such mice die of [illegible]
despite [illegible]
when in [illegible]
they die [illegible]
to a highe[illegible] which invariably survive
(table 7) With the virus of St Louis encephalitis, the greater cellular vulnerability was still evident at 3 to 4 weeks of age, but not in older mice (table 8)

The possibility that cellular vulnerability may itself be influenced by genetic factors as well as by age, came under consideration when the French neurotropic strain of yellow fever virus was found to produce fatal encephalomyelitis in a certain proportion of PRI mice of any [illegible]
the fact that [illegible]
as in those
with certain [illegible] and St Louis encephalitis
Since the multiplication-depressing factor is inherited as a dominant,

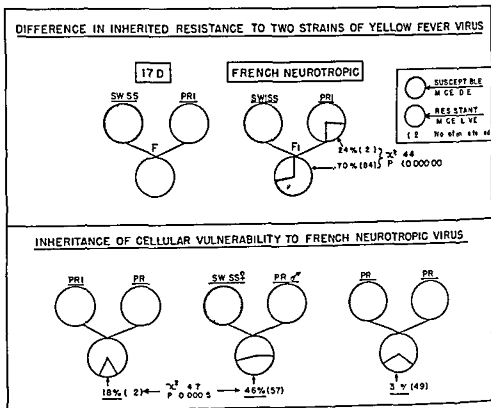


Fig 3

it was possible to study the effect of crossing PRI and Swiss mice on cellular vulnerability without affecting the level of virus multiplication The results shown in figure 3 indicate that the F_1 progeny were markedly more susceptible to the French neurotropic yellow fever virus than the unselected PRI mice Additional information on the genetic aspects of cellular vulnerability was obtained by mating PRI males of proved resistance either with Swiss females or with PRI females subsequently proved to be either susceptible or resistant to the French neurotropic yellow fever viru While the results shown in figure 3 are based on death and survival the effect on cellular vulnerability was not of the all or none variety since a small proportion of the mice developed weakness or paralysis of the extremities but did not die The fact that PRI parents of low cellular vulnerability (i e resistant) produced 18 per cent of progeny with high cellular vulnerability suggests that the latter character might involve recessive genes and that the PRI stock is heterozygous in this respect although homozygous for the multiplication depressing factor More work needs to be done on this phase of the problem before it is possible to make a genetic analysis of the factor responsible for cellular vulnerability

TABLE 9

Occurrence of variant strains of virus capable of overcoming inherited resistance of host

Virus	Strain	No. of passages in Swiss mice	Behavior in PRI mice		Peak multiplication in brains of Swiss mice
			Mortality	Peak multiplication in brain	
			%		
Japanese B encephalitis	Korea	4	13	2 4 3 0 3 8*	8 0*
	Nakayama	43	50	3 3	7 8
	Nakayama	±70	100	7 6	9 3
St. Louis encephalitis	Winkler	8	6	9 6	7 8
	Webster No. 3	Hundreds over 17 years	90	4 2	9 0

* Reciprocal of log of LD_{50}.

Virus variants capable of overcoming effect of genetic multiplication-depressing factor

Tests on different strains of the same virus or different passage levels of the same strain have shown that virus variants may occur which can overcome the inherited resistance of the host either by multiplying at higher levels despite the inhibiting effect of the genetic multiplication-depressing factor or by producing greater cellular damage at low levels of viral multiplication in mice that are not full grown (table 9).

Observations on possible role of genetic factors in human poliomyelitis and yellow fever

As early as 1898 Taylor (7) suggested that certain families exhibited a special predisposition to the paralytic consequences of poliomyelitis. Similar observations have been made in a number of subsequent reports (8 9 10 11). Addair and Snyder (12) in an especially interesting study on the family relationships of every case of paralytic poliomyelitis over a period of 50 years in a relatively isolated county in West Virginia, concluded that an autosomal recessive gene probably played a role in susceptibility. The recent study of Herndon and Jennings (13) ...

... infection with poliomyelitis virus. Masimi (14) in a recent report of ...

TABLE 10

Some examples of exceptionally high poliomyelitis paralytic attack rates in relatively isolated inbred populations

Region	Year	Size of population	Attack rate per 100 000*
Chesterfield Inlet—Arctic Eskimos	1949	275	21,000
Nicobar Island, India	1948	10,000	8,000
Sukkertoppen, Greenland	1944	700	5,300 fatal (many more paralyzed)
Sukkertoppen, Greenland	1932	700	2,400
Kangamiut, Greenland	1932	300	4,300
Holsteinborg, Greenland	1932	400	4,000
St Helena	1945	4,000	1,990
Guam	1899	8,000	808 (many more paralyzed)

* The rate per 100 000 is given to permit easy comparison with rates of 20 to 100 obtaining in usual epidemics in U S A

statistically significant It has also occurred to me (11) that the most plausible explanation for the exceptionally high paralytic attack rates among certain relatively isolated, highly inbred populations is that it represents instances of primary infection in populations of special genetic susceptibility (table 10)

The highly endemic areas of yellow fever in Africa are for the most part inhabited by population groups which are uniformly resistant to yellow fever in the sense that they do not suffer from the severe clinical manifestations of the disease Strangers coming to these areas usually succumb with the severe form of the disease It is more than probable therefore, that thousands of years of exposure to this infection have eliminated the individuals carrying the recessive genes for susceptibility, resulting in a race possessing the dominant genes for resistance The mixed occurrence of severe and mild infections among the South American Indians is in accord with the hypothesis that yellow fever was imported from Africa after the discovery of America, not enough time having elapsed for the virus to kill off a significant number of those carrying the recessive genes for susceptibility

SUMMARY

1 Experimental studies on mice have shown that resistance or susceptibility to certain viruses affecting the nervous system can be inherited

2 Resistance to the 17 D strain of yellow fever virus was found to depend on dominant, autosomal genes which depress the level of viral multiplication to $\frac{1}{10{,}000}$–$\frac{1}{100{,}000}$ of that occurring in susceptible mice

While the results of interbreeding experiments are in accord with the Mendelian laws for a single pair of autosomal genes, it has not been ruled out that multiple genes, with a small amount of crossing over, may be responsible for this factor

3 The genetic multiplication-depressing factor controls something so specific that one group of viruses (i e , yellow fever, dengue fever, West Nile fever, Japanese B, St Louis, and Russian encephalitis) is affected by it while others (e g , Western, Eastern, and Venezuelan equine encephalitis poliomyelitis rabies, etc) are not

4 The genetic multiplication-depressing factor is localized in the susceptible cells

5 High cellular vulnerability at low levels of viral multiplication can abolish the resistance imparted by the inherited multiplication-depressing factor For some viruses high cellular vulnerability is a function of age, for others it may depend on genetic factors

6 Certain virus variants can overcome the inherited resistance of the host either by multiplying at higher levels despite the inhibiting effect of the genetic multiplication-depressing factor, or by producing greater cellular damage at low levels of viral multiplication in hosts that are not full grown

DISCUSSION

DR C [illegible]
very fun [illegible]
which par [illegible]
data bear [illegible] status are presented indicating that the genetic resistance is due to the ability of the host to depress the reproductive level of the virus This could well be a pattern of wide applicability to other disease con [illegible]

[illegible] hereditary or even [illegible] the door is closed and nothing practical can be done from [illegible] viewpoint Nothing [illegible]
is only the first st [illegible]
the m [illegible]

environmental components of the susceptible status This work is only a first step but if the mechanism of action of the genetic component could be elucidated further and the genetically susceptible children identified there would be obvious advantages in prevention of paralysis Work with gamma globulin and vaccines could then be concentrated on the constitutionally susceptible Many examples could be quoted to demonstrate that fundamental genetic research of the type presented so ably by Dr Sabin may have important results in application to disease prevention

Dr A B Sabin (Closing) In connection with Dr Herndon's remarks about poliomyelitis I should like to say that certain epidemiologic observations as well as results of recent studies in my laboratory on variation in virulence of poliomyelitis viruses lead me to believe that the genetic factors which influence variation among the poliomyelitis viruses are of much greater importance in determining the paralytic consequences of infection than are the genetic factors of the host By special methods of cultivation and selection we have recently succeeded in converting highly virulent (paralyzing) strains of each of the 3 immunologic types of poliomyelitis virus into avirulent (nonparalyzing) variants

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CHAPTER V

THE INHERITED AND ACQUIRED COMPONENTS OF BEHAVIOR

ANNE ANASTASI

Discussions of the relative contribution of hereditary and environmental factors to behavioral characteristics are often weakened by inadequate clarification of the underlying concepts. Superficial, confused, and ambiguous notions regarding the nature and operation of both heredity and environment may account for much of the controversy in this area. It would thus appear desirable to re-examine the conceptual framework within which behavior data pertaining to heredity and environment are interpreted.

In what sense can *heredity* be said to influence behavior? In so far as hereditary factors contribute to individual differences in behavior, the contribution is necessarily indirect. Heredity may influence the development of structural or organic characteristics, which in turn may impose certain limiting conditions upon behavior development. A cat cannot learn to fly because it has no wings. If a child has a defective thyroid, his movements will be slow and sluggish, and his general behavior dull and stupid. For the development of certain types of behavior, vocal organs, hands, and a human nervous system are essential prerequisites. Similarly, a number of behavioral anomalies may be traced to glandular defects, pathological brain conditions, chemical deficiencies, and the like.

The presence of certain organic characteristics, however, should be regarded as a necessary but not a sufficient condition for the development of any specific type of behavior. In other words, the fulfillment of the organic prerequisites does not in itself insure that the given behavior will appear. It also follows that the absence of a given type of behavior does not necessarily imply an organic deficiency, nor do behavioral variations always imply corresponding organic variations. Except for individuals with gross pathological defects, the organic equipment of most persons is such as to permit an almost unlimited variety of behavior development.

In the interpretation of behavioral differences, the distinction between hereditary and environmental etiology is often confused with that between organic and experiential etiology (cf. 2, 3, ch. 4). The term "ex

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environmental components of the susceptible status This work is only a first step but if the mechanism of action of the genetic component could be elucidated further and the genetically susceptible children identified there would be obvious advantages in prevention of paralysis Work with gamma globulin and vaccines could then be concentrated on the constitutionally susceptible Many examples could be quoted to demonstrate that fundamental genetic research of the type presented so ably by Dr Sabin may have important results in application to disease prevention

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540–554 1939

fail to meet the criterion of constitutional even in the restricted sense of demonstrated organic origin

We could of course adopt the facile expedient of classifying such un differentiated aments after the fashion of Tredgold (25) In that classic work on feeblemindedness confusion is further compounded by introducing the concept of primary or endogenous amentia Under this category, Tredgold includes a few varieties whose hereditary origin has been demonstrated some of the varieties for which the bulk of the evidence suggests prenatal environmental etiology, and all undifferentiated amentia, which is assumed to be hereditary since its etiology is unknown Yet it is undifferentiated amentia which offers the most challenging opportunity for investigating the role of experiential factors Although organic bases will undoubtedly be discovered for some of the cases now included in the undifferentiated category it is likely that psychological factors in the individual s early environment will be found to play an important part in the etiology of many cases of simple amentia

Another concept which has been the source of much confusion is that of *maturation* (3 ch 4) Usually contrasted with learning, maturation connotes the development of specific behavior in the absence of any opportunity for learning such behavior If adequate control procedures have been followed to assure that all opportunities for relevant learning have been truly excluded we can conclude that whatever behavior appears is unlearned But unlearned is not synonymous with hereditary' When defined operationally unlearned behavior can only mean behavior which is wholly determined by organic characteristics so that the mere presence of the organic prerequisites insures the appearance of the behavior in question The term maturation however suggests a positive explanation or active process which accounts for the behavior development At the same time the evidence usually cited in support of maturation demonstrates only the absence of learning it does not generally provide information about the specific structural factors which account for such behavior Nor does it indicate whether the prerequisite structural factors are themselves traceable to hereditary or environmental conditions

A word may also be added regarding the glib statements often made about the inheritance of *intelligence* Such statements illustrate not only the fallacy of misplaced concreteness (cf 7) but also the use of descriptive categories which conflict with available data on the nature and organization of psychological traits Intelligence is an abstraction—and a rather poor one—arising out of our efforts to describe behavior It does not correspond to any single behavioral entity Because it has so many meanings the word intelligence has no single logical meaning Specialists

periential' as herein employed is simply a convenient adjective with which to designate the individual's preceding reactional biography It also refers to the concept of learning in its broadest sense, and is synonymous with some of the meanings of the terms 'functional' and 'psychological' (cf 12)

From both a theoretical and a practical point of view, the distinction between organic and experiential etiology of behavior is an important one It is well to bear in mind, however, that this distinction is not the same as that between heredity and environment Thus organic characteristics can themselves result from either hereditary or environmental factors Examples of hereditary organic etiology are provided by amaurotic idiocy and phenylpyruvic amentia Environmental organic etiology is illustrated by mental defect associated with cerebral birth lesions, as well as by behavior impairment arising from nutritional deficiencies or other abnormalities of prenatal environment

The common confusion between the hereditary environmental dichotomy and the organic experiential dichotomy is exemplified by the varied uses of the term '*constitutional*' Sometimes this term is used to mean simply organic, at other times it also seems to imply hereditary In a well known definition of feeblemindedness, constitutional origin of the condition is made an integral part of the concept of feeblemindedness (6) According to this definition, intellectual and social inadequacy which cannot be shown to have a constitutional origin must be regarded as pseudo feeblemindedness If, now, constitutional in this definition implies hereditary, then the large majority of persons in institutions for the feebleminded could not be considered truly feebleminded Any cases of mental deficiency resulting from conditions in the prenatal or postnatal environment would have to be excluded from this designation

Incidently, such a definition of feeblemindedness would also eliminate by fiat all research on the contribution of environmental factors to the development of feeblemindedness Any data demonstrating the role of specific environmental factors in the etiology of mental deficiency would have to be interpreted as showing that the condition investigated could not have been true feeblemindedness in the first place

If, on the other hand the concept of constitutional origin is dissociated from heredity and is considered to be synonymous with organic etiology then all the so called special clinical varieties of feeblemindedness would be included in the given definition This certainly seems to make more sense There still remains however the type of feeblemindedness which has been variously described as simple subcultural undifferentiated familial, or garden variety mental deficiency (12 15 25) This condition which represents the largest single variety of feeblemindedness would

the adult community. He thereby gains training and experience in leadership situations which in turn increase his qualifications as a leader.

Any discussion of the concept of environment must also take into account the growing body of evidence on the importance of prenatal environment. The role of various prenatal physical conditions in the etiology of feeblemindedness has been widely discussed and investigated. The well-established fact that organisms respond to stimulation during the prenatal period is likewise relevant to an understanding of their subsequent behavioral development (10). Nor can we ignore the possibility that simple learning may occur prenatally (8, 11, 19, 20, 21, 29).

The *interrelation* of hereditary and environmental factors also merits further consideration. The concept of interaction has now generally replaced the earlier view that behavior could be classified into that which was wholly determined by heredity and that which depended entirely upon learning. It is not always recognized, however, that interaction should be differentiated from the additive combination of hereditary and environmental factors (2, 14). For example, generalized estimates of the proportional contributions of heredity and environment to any given behavioral characteristic imply an additive combination, which is inconsistent with the concept of interaction.

Any one hereditary factor may operate differently under different environmental conditions. Similarly, any given environmental factor may exert a different influence depending upon the specific hereditary characteristics of the individual. Such an environmental factor as a radio in the home, for example, will not have the same stimulus function for a deaf and a hearing child.

As another illustration, let us consider two homes chosen so as to typify opposite extremes with respect to the opportunities they afford for intellectual development. One represents a Kallikak type of environment, providing only the bare necessities for survival; the other meets all the specifications recommended by the child psychologists and educators. It can be assumed for the present purpose that agreement could be reached on such recommendations. Let us now suppose that two identical twins are separated shortly after birth and each is reared in one of these two homes. We would thus have a large and clearly specified environmental difference operating upon two individuals of identical h

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in the construction of psychological tests have been making repeated efforts to bring about the abolition of the term intelligence' Statistical studies of test results, utilizing the techniques of factor analysis have shown that intellectual functions are organized, not into a single intellective factor, but rather into a number of relatively independent traits (cf 3 ch 15, 23, 24) Moreover, the number and nature of such traits are themselves influenced by the individual's reactional biography (1, 3 ch 15)

So far this discussion has been concerned with the concept of heredity as it pertains to the domain of behavior The concept of *environment* also needs re examination (cf 2) The psychological environment includes more than the individual's home address Residence in the same home does not connote identity of environment, nor does geographical separation necessarily imply an increase in environmental differences Two children reared in separate homes—such as identical twins adopted by different families—may be exposed to more closely similar environments than two siblings living in the same home It is necessary to consider not only such obvious conditions as socio economic level and educational opportunities, but also more subtle factors such as sibling and parent child relations Moreover the same environmental condition may have dissimilar stimulus functions (cf 12) when encountered by individuals at different age levels

Studies based upon familial correlations and analyses of family history data are complicated by the fact that the human family is a cultural as well as a biological unit In general the closer the hereditary relation between persons in our culture the greater is their environmental proximity Consequently the same hierarchy of behavioral correlations could result on the basis of either heredity or environment so that the explanation of obtained family resemblances remains ambiguous Assortative mating with respect to many psychological characteristics further complicates the picture

The role of social expectancy and social stereotypes is also of interest in interpreting some of the data on sex differences race differences and constitutional types For example certain correlations between body build and behavior characteristics have been reported in support of theories of constitutional types such as that of Sheldon (16 17) Rather than being of constitutional origin, however the observed differences in behavior characteristics may have developed in response to the differential social treatment received by individuals of differing physique (3 ch 13 4 5) Thus the taller, more athletic mesomorph conforms more closely to the popular stereotype of the leader As a result such an individual is more likely to be accepted as a leader—in school, in college and eventually in

logical factor in the environment, they conclude that the behavior characteristic must have a hereditary origin—and there the search ends. The course of science will not be advanced by using the concept of heredity as a substitute for an admission of ignorance.

DISCUSSION

DR. FRANK A. BEACH [New Haven, Conn.]: Many of the things Dr. Anastasi has said are

profoundly influenced by genic factors or is instead shaped principally by nongenic forces, is of little or no importance *unless* one is interested in two or more *generations of individuals*. As *several geneticists* present at this meeting have said again and again, genetically controlled characters are not necessarily unmodifiable (in the individual) and environmentally determined traits often prove exceedingly resistant to change.

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itself depend upon the individual characteristics of the twins under consideration.

The more precisely heredity and environment are defined and the more fully their operation is investigated, the more evident it becomes that they are inextricably intertwined. The very distinction between them no longer appears as sharp as it once did. In the study of behavior, the distinction between organic and experiential etiology seems to have more promise, from both a practical and a heuristic point of view. Since heredity must necessarily operate through the medium of structural or organic factors, it follows that the applicability of the concept of heredity to behavior phenomena is indirect and remote.

It should also be borne in mind that heredity and environment are themselves abstractions. Each covers a multiplicity of factors which interact with each other. It is not enough to conclude that Environment caused a particular behavior deviation. We must know what specific factors in the environment brought it about. Similarly, when we attribute a given behavioral characteristic to Heredity, we have not solved the problem, we have only formulated a problem. We must find out *what* is inherited. What is the hereditary condition which ultimately and indirectly leads to this behavior deviation, and how does it operate in bringing about the behavior under consideration?

When selective breeding investigations suggest that maze learning ability is inherited, we still do not know what is actually being transmitted through heredity (26). It obviously cannot be maze learning. That is not a characteristic of rats; it is something rats are called upon to do when they meet psychologists. Are the obtained differences in maze learning performance between the experimentally bred groups of rats the result of differences in emotionality, motivation, speed of running, general activity level[2], body weight, brain size, or some other intermediate characteristic? The answers to this question which have been provided by the available experimental data have so far proved somewhat contradictory (9, 18, 22, 26, 27).

The same type of question needs to be asked about any results pertaining to the inheritance of a behavior characteristic, whether it be fighting behavior of mice, human feeblemindedness, or musical aptitude. Failure to follow through in this manner accounts for the all too common practice of attributing to heredity any behavior characteristic whose etiology is unknown. When some investigators fail to discover any etio

[2] The aforementioned characteristics, all of which have been proposed as possible factors to explain selectively bred differences in maze learning, are themselves expressed in behavioral terms. Hence they in turn need to be correlated with structural factors which can be more directly traced to hereditary conditions.

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Instead of asking pointless and unanswerable questions concerning the 'learned' or the 'acquired' nature of different types of behavior, psychologists are beginning to address themselves to more meaningful queries. These are usually of the following types: (1) what correlations can be demonstrated between a given aspect of behavior and the genotype, (2) how are relationships between the gene or genes and behavior mediated, and (3) in what ways do nongenic factors contribute to relationships between the genes and behavior?

The answers, when we get them, will inevitably reflect many indirect and complex relations between genes and psychological variables. To doubt this is actually to question the fact that the individual's behavior is dependent upon the behavior of the cells, organs and organ systems of which he is constructed.

DR. J. P. SCOTT [Bar Harbor, Maine]: I would like to add a brief comment on a concept which has been brought up in connection with this paper and also in earlier papers this morning: the concept of interaction.

In the strict sense of the word, interaction means that two or more factors modify or change each other. I would like to point out that interaction in this sense does not exist with regard to heredity and environment because in any given individual the genes are well protected from environmental effects. The situation may be better described as co-action or counteraction. Both the genes and the environment modify a substrate, which in this case is behavior, and their action may be to work together (co-action), or they may work in opposite directions and so may be said to counteract each other. This does not detract from what Dr. Anastasi has said or the conclusions she has reached because I believe that she has used interaction in another sense. I do wish to make the matter clear because I do not think that any geneticist, with the possible exception of Lysenko, believes that environment has a direct effect on the heredity within an individual. Radiation may produce mutations but these have no relation to the causal agent and their effects may not be seen until future generations.

There are, however, cases of long time true interaction between heredity and environment. A given species of animal living in a certain environment may modify or select its environment by its behavior. This in turn may result in a change in the direction of natural selection which, of course, will modify the genetic composition of the species. This is a real case of interaction in which the genes influence behavior, behavior modifies environment, and the environment in turn modifies the gene. But this sort of thing does not occur within the lifetime of an individual. Nevertheless, the very complicated effects which Dr. Anastasi has mentioned do occur and can be accounted for as a result of what may be more strictly called co-action or counteraction.

DR. ANNE ANASTASI (Closing): I have very few comments I want to make. I agree heartily with everything that Dr. Beach said. As for the last point on interaction, I think that the sense in which interaction is used here is very similar to the statistical sense of Fisher's interaction variance. It simply means that we have to take into account the fact that the same influence will operate differently under different conditions. The same environmental influence, for example, will operate differently under different hereditary conditions, and the same hereditary influence will operate differently under different environmental conditions. We cannot simply state the proportionate contribution of one or the other without also taking into account an interaction term. It is not that one modifies the other, but that the relative effects of each factor vary as the other factor varies.

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Fig 4 Brain from a lamb which showed symptoms of ataxia (left) For comparison a brain from a normal lamb (right)
Courtesy of Drs P A Palsson and H Grimsson and the Proceedings of the Society for Experimental Biology and Medicine

Innes has described the pathologic changes of this congenital demyelinating disease (10) There occurs a marked loss of myelin and cavitation takes place in the white matter Chromatolysis may be found in the nerve cells the red nucleus is a site of predilection for such cell degeneration

There is good evidence that this severe cerebral damage is due to copper deficiency Eden and coworkers (4) found the blood copper content reduced in ewes from affected areas, Bennett and Chapman (1) in Australia and Dunlop and coworkers (2, 3) in England could reduce or eliminate the anomalies by feeding copper to pregnant ewes

Identical findings were recently reported by Palsson and Grimsson from Iceland (12) The farmers along the coast graze their sheep on seaweed during the winter Ewes are most prone to give birth to affected lambs when fed seaweed during the last half of the gestation period The blood copper level of the ewes is about one fifth of normal and livers from affected lambs have a copper content which is 20 to 30 times lower than the normal average Feeding copper sulfate to pregnant ewes reduces the incidence of the anomaly in the young

It is not yet known why a deficiency of this metal leads to such severe cerebral defects but the facts appear established and should be kept in mind during the discussion of the following subject

A congenital disease picture occurring in man and attributable to pre

CHAPTER VI

PRENATAL EFFECTS OF NUTRITION ON THE DEVELOPMENT OF THE NERVOUS SYSTEM

JOSEF WARKANY AND J. G. WILSON[1]

A discussion of the prenatal effects of nutrition is somewhat out of place in this symposium on Genetics and the Inheritance of Neurological and Psychiatric Patterns, but whenever one set of factors is stressed in the explanation of biological events it can do no harm to recall that other factors must not be neglected.

Many experiments have demonstrated in recent years that the normal development of the embryo depends upon its normal nutrition. It could also be shown that specific structural changes of the embryo can be induced by specific dietary deficiencies (16). It is unfortunate for our present assignment that those experiments which have been performed on a large scale and which have been confirmed in many places have not resulted in marked changes of the nervous system.

It seems preferable, therefore, to use the short time available for a review of two nutritional experiments of nature, each of which resulted in anomalies of the central nervous system. Such experiments of nature are not as clear cut as experiments planned in the laboratory; they are not free from accessory and interfering factors, but they are the more convincing since they show that the nervous system can be harmed by nutritional deficiencies occurring in a natural environment.

The results of prenatal copper deficiency have been described in lambs. In Australia and England a disease called enzootic ataxia or swayback occurs in sheep which feed in pastures said to be deficient in copper (1, 2, 3). The young of such ewes show spastic paralysis, lack of coordination and sometimes blindness. The incidence of affected young varies in different flocks but it has been as high as 90 per cent. The brain of the abnormal lamb is smaller than that of normal newborns and the hemispheres appear to be collapsed. The cerebral cortex is thin, the convolutions are flattened and poorly defined (fig. 4). The changes are even more marked on frontal sections. One sees large cavity formation due to destruction of the white substance, the gray matter remaining relatively well preserved (fig. 5).

are very flaccid resulting in poor posture and hernias Sexual functions are usually absent in the male but cretinous women may become pregnant and do so quite often As a rule the body temperature is low

However not all the symptoms of such patients can be attributed to thyroid dysfunction Associated malformations are not rare Hydrocephaly, strabismus eye defects urogenital anomalies and club foot are more frequent than in non-cretins (5 13)

The mental development is always subnormal but there are many gradations between full-cretins and idiots and half-cretins and borderline cases In endemic areas the incidence of mental deficiency is about three times as great as in non-endemic regions Typical cretins are dull childish apathetic usually good natured and obedient Occasionally they are irascible depressed or aggressive (13) Some are of such low mentality that they can not be admitted to institutions Cases of average severity are found in poorhouses or in institutions for the feeble minded Half-cretins can be employed on farms in the house or in the fields where they are entrusted with menial tasks

Various neurologic abnormalities are found Cretins are often recognized by their abnormal posture and clumsy gait Spastic diplegia or paraplegia occurs in some of the severe cases Deafness and speech defects are almost universal



Fig 6 Full ... cretin from Switzerland Courtesy of Dr Hans Eggenberger



Fig 5 Series of coronal sections of the same brains as in figure 4 *Upper row* Sections of abnormal brain showing marked bilateral cavitation and some dilatation of the lateral ventricles *Lower row* Sections of normal brain

Courtesy of Drs P A Palsson and H Grimsson and the Proceedings of the Society for Experimental Biology and Medicine

natal nutritional deficiency is endemic cretinism This condition occurs in many regions of the world and has been known for several centuries It has become so rare in the United States that it will be necessary to give a short description of its clinical and epidemiological features

Endemic cretinism occurs in areas where goiter is endemic Figure 6 shows a cretin from Switzerland These people are easily recognized as endemic cretins if they have enlarged thyroids This distinguishes them from sporadic cretins who are characterized by congenital aplasia of the thyroid gland Sporadic cretins are well known in this country but the etiology of this congenital malformation remains unexplained In endemic cretins a thyroid gland is always found it may be enlarged as in the goitrous case shown in figure 6 or it may be atrophic and seen only on operation or autopsy Such atrophic thyroids are small fibrous calcified to a large extent and contain few functioning follicles Whether goitrous or not, these people have signs of thyroid deficiency Myxedema is usually well developed and many of the patients are dwarfed The skeletal maturation is retarded epiphyseal *dysgenesis and deformities of the joints are not rare* The muscles

of endemic cretinism The outcome of this great experiment undertaken in previously endemic areas should become known in the near future

It must be admitted, however, that objections have been voiced against the iodine deficiency theory (8) There are *inconsistencies and weaknesses* in its structure which can not be discussed here Carotene (9), fat, and protein deficiencies have been brought into the discussion, and positive goitrogenic factors have also been considered

Both endemic goiter and cretinism have been regarded as hereditary conditions They can be transmitted from generation to generation, and identical twins concordant in regard to goiter or cretinism, have been observed It is not surprising that some authors declared the cretins to be degenerated rests of a primitive race of man' (7) But such statements can not be taken seriously All critical studies demonstrate that endemic goiter and cretinism are due to environmental factors which are closely bound to certain localities These adverse factors affect the mother and through her the unborn child Heredity plays no decisive role in these co[illegible]

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The cerebral changes vary a great deal In the reports of the nineteenth century, gross anomalies of the brain were frequently described Asymmetry of the hemispheres, underdevelopment of entire lobes convolutional anomalies, marked wasting of the white with preservation of the gray matter, and internal hydrocephaly were repeatedly described in the older literature (14) In recent studies such gross changes have not been found but microscopic developmental anomalies have been recognized Lotmar (11) made a thorough study of the finer structure of the cerebral and cerebellar cortex of 14 cretins from Bern, Switzerland He found irregularities in the development of the various cortical layers and variations of nerve cell distribution In some instances ectopic nests of nerve cells were found in the molecular layer of the cerebral cortex and occasionally atypical giant pyramidal cells were seen In the cerebellar cortex ectopic Purkinje cells were found displaced into the molecular layer Recent investigators agree with the older ones that the cerebral changes are prenatal in origin and date back to fetal life

Endemic cretinism occurs on all continents and in many races It is limited to certain areas and never appears in the absence of goiter endemias In such areas it is estimated that about one half of one per cent of the population are cretins In one village where more than 55 per cent of the population had goiters Eugster (6) found an incidence of cretinism of 3 5 per cent In 1928 Eggenberger (5) estimated that there were about 5 000 endemic cretins in Switzerland who had to be maintained in institutions at public expense There is general agreement that the mothers of all cretins have goiters and that the cretins acquire their thyroid disturbance and some of their cerebral anomalies *in utero* Treatment with thyroid preparations after delivery reduces the manifestation of hypothyroidism but mental deficiency and deafness can not be influenced Endemic cretinism must be combatted by prevention of the maternal goiter and the gestational insufficiency which goes with it

The etiology of endemic goiter is probably complex The iodine deficiency theory which is now over one hundred years old is most widely accepted Its adherents assume that lack of iodine in water soil and food leads in certain areas to an endemia of goiter While these goiters are compatible with euthyroidism they may become insufficient during pregnancy and cause damage to the developing fetus The defects of the injured fetus who later becomes the endemic cretin are therefore indirectly due to the iodine deficiency of the mother This theory is so widely accepted because it proved to be heuristic It led to the recommendation of iodized salt for prophylactic purposes a measure which proved very successful in most endemic areas where it resulted in disappearance of goiter particularly in children (5) The offspring of this new goiter free generation should be free

een much written to the effect that starvation affects neuron structure, but I would caution hat postmortem changes which appear in less than an hour are more marked than any histological alterations due to inanition

To what extent the fetal and newborn brain may be damaged by inanition, we really do not know Perhaps some of the defects seen in the brain of the newborn and associated with deficiencies of certain trace elements vitamins or hormones may really be changes brought on indirectly by anoxia The changes which you demonstrated in the lantern slides, due to copper deficiency in the ewe and thus in the lamb, resemble certain changes which we could induce in guinea pigs suffering asphyxiation at birth

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birth to children without goiter Conversely, it has been observed that healthy persons moving into endemic areas may develop goiters Eugster (6) has demonstrated in careful studies that inbreeding does not influence the incidence of goiter and his observations of cretin twins do not suggest any hereditary disposition to endemic cretinism

However, it must be mentioned here that genetic factors are probably responsible for a rare type of goitrous cretins who are clinically indistinguishable from endemic cretins Stanbury and Hedge (15) described four sibling cretins with goiters living near the sea coast of Massachusetts an area where dietary iodine deficiency does not occur These children one of whom is illustrated in *figure 7*, were deficient in thyroid hormone because their thyroid glands could not convert iodide into an organically bound form It seems that in such patients one of the steps in hormone synthesis is blocked This rare disease picture was found in four of seven siblings Their parents were normal and intelligent, but were first cousins It seems likely that in these cases the cretinism was due to an inborn error of metabolism which was genetically determined Thus cretinism with goiter is due to nutritional deficiency in the majority of cases, but in rare instances to an inborn error of metabolism This is a good illustration of the principle too often forgotten by analysts of human diseases, that one and the same disease picture may be genetically determined in some cases and environmentally in others Rickets furnishes a comparable example Thirty years ago most cases of rickets could be attributed to unfavorable living conditions, lack of sunshine and vitamin D Since this form of rickets has been eradicated, it has been recognized that there still exist some rare types of rickets which are resistant to vitamin D there is increasing evidence that many of these residual cases are genetically determined Cataract may also be of differing etiology it is inherited in some cases in others it is due to rubella of the mother in early pregnancy

To the geneticist endemic cretinism of nutritional origin represents a 'phenocopy of the hereditary form to the ecologist, the goitrous cretin who suffers from an inborn inability to utilize available iodide represents a genocopy of the endemic form The differing viewpoints and terminology do not matter as long as one remembers that many if not most of the disease pictures encountered in human pathology are symptoms of abnormal development, but not necessarily disease entities of the same etiology

DISCUSSION

DR WILLIAM F WINDLE (Bethesda Maryland) Mr Chairman I might add a little to this My group has been interested in affecting prenatal development by altering the internal environment of the fetus

One of the surprising results of our experiment was that extreme inanition of starvation failed to alter the guinea pig's brain histology to any appreciable extent I know there has

Part II

NEUROLOGICAL AND MENTAL PATTERNS AND THEIR INHERITANCE

CHAPTER VII

THE PHYLOGENETIC DEVELOPMENT OF BEHAVIOR PATTERNS

LEONARD CARMICHAEL[1]

The interspecies comparison of adult or of developing patterns of behavior is a field of study that presents many difficulties. For example, only the novice in this area is willing to take from comparative anatomy a description of a series of brains from the dogfish to man and then attempt to show a one-to-one correlation between this anatomical series and measured aspects of adaptive behavior.

For many years those studying the growth of behavior responses in the animal series have attempted to summarize this process by a number of generalizations or so-called laws.

The biogenetic law, or recapitulation theory, is the name given to one of these attempts (1). This proposal of Ernst Haeckel, which asserts that the life history of the individual is a condensed resume of the life history of its ancestral forms, or more briefly, that ontogeny (development of the individual) repeats phylogeny (development of the race), is no longer accepted as a general law in biology. The parallelism between the evolution or ascent of the animal series from the single-celled organism to the mammal and the growth of each individual from a single cell to its adult form cannot, however, be wholly neglected. In the study of behavior this ...

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t ... in various ways passes through behavior stages typical of prehistoric or savage man has now generally been abandoned. A comparison, however, of the development of the unlearned behavior of early fetal life of a mammal and the adult behavior of less complex organisms nevertheless presents some interesting points for consideration.

If the recapitulation theory in a simplified form were true, it would only be necessary to map one single story of growth for all embryonic and fetal behavior and then to note the particular level, as it were, on the escalator of development at which each species steps off. While in detail of course no idea of the phylogenetic development of anatomical structure

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synthetic terms This means that each course of behavior growth must be studied for itself and cannot be deduced in advance of the facts of observation from generalizations about any all inclusive processes such as individuation or integration It must be noted however, that there is much evidence in favor of Hooker's view that the broad concept of an expanding total pattern from which specific local activities are derived is not only typical of Amblystoma with which Coghill worked so extensively but also of the mammals

Similar criticisms may be lodged against some other general descriptions of the growth of behavior The suggestion that organisms develop their effective responses first in the head region and that such activities then move sequentially toward the tail is illustrated by many examples in behavior growth but is not universal in its applicability This so-called law of the cephalocaudal course of behavior growth has of course, a certain parallelism in morphological embryology

The proximodistal law of development that is, the generalization that the movement of the extremities begin with the activities of large muscles near the trunk and that effective response then progresses to the smaller muscles at the end of the limbs is also a summary of development in time This rule although sustained by a good deal of evidence is like the other so called laws mentioned *not universal*

In comparisons of behavior patterns in terms of their phylogenetic development or of their neurological basis it is important from the outset therefore that the experimenter take such hints as he can from existing generalizations but he must not let himself be unduly influenced by them in his reports of observations The slow process of amassing rigorously controlled quantitatively *described* facts about the onset and change of behavior systems in *particular* species of organisms during measured developmental periods is still the only sure approach to this comparative problem

Two principles of limited *significance* however to

present writer the *principle of anticipatory maturation* (7) This still tentative generalization suggests that all or almost all functions in a wide variety of organisms can be elicited by experimental means *before the time when in the* development of the organism the response in question first normally becomes operative In other words biological activities needed to advance the economy or even to preserve the life of the individual at certain stages of development are commonly waiting and ready in the wings of the theater of life, as it

or of behavior could be more misleading than this suggestion, it must be remembered that the recapitulation point of view can sometimes suggest leads for the observer of specific fetal patterns of activity

Another attempt at generalizing about growth is found in the contrasting theories of *individuation* and *integration* Even before the epoch making work of the late G E Coghill some students of behavior felt that the evolution of certain patterns of response in the individual could be described as a change from the general to the particular This was spoken of as the passing from a relatively indefinite, incoherent, homogeneity to a relatively definite, coherent, heterogeneity of response

This point of view was adumbrated for example in the nineteenth century by the great German physiologist Preyer (2) It was developed both in regard to behavior and to its neurological basis, by Coghill and has come to be called the theory of individuation of behavior Coghill himself stated this theory as follows The behavior pattern from the beginning expands throughout the growing normal animal as a perfectly integrated unit, whereas partial patterns arise within the total patterns and by a process of individuation, acquire secondarily varying degrees of independence Complexity of behavior is not derived by progressive integration of more and more originally discrete units (3)

According to this schema, behavior begins in large general movements As morphological development continues these overall patterns such as total trunk flexions gradually become more and more individuated and eventually constitute specific reflexes and other definite patterns of behavior Dr Davenport Hooker a most careful and perceptive student of human fetal behavior has discussed the value and limitations of this principle as descriptive of the growth of man s earliest responses (4)

Opposed to this point of view is the suggestion that complex integrated biologically useful patterns of adult behavior are ordinarily put together from earlier more discrete and simpler responses Dr W F Windle has clearly pointed out how specific are the early responses of some of the fetal organisms he has so ably studied (5) This theory in its general form has come to be spoken of as the integration theory of the growth of behavior

Various modifications of these two somewhat opposed views have been suggested In one context for example the late I P Pavlov wrote of initial decomposition of the whole into its parts or units and then the general reconstruction of the whole from these units or elements (6) Many students of the growth of behavior have now come to the conclusion that at least after learning or the modification of behavior by the environment begins adaptive behavior must be considered both in analytical and in

in mammals and birds illustrate such a comparison Growth in an egg developing outside the maternal organism's body differs in many ways from growth of the embryo and fetus in the mammalian amniotic sac (12) The rhythmic beating of the amnion in the egg regularly tosses the growing chick embryo as it develops General maternal bodily movements in a different but comparable way influence the growing fetal mammal

It is also true that the total length of fetal life before birth or hatching is a significant factor in the development of behavior patterns This illustrates well the complex considerations that must be dealt with in arriving at a valid comparison of different species At birth some behavior mechanisms must be present and effective if the young organism is to survive Among the fundamental patterns of response required to be in a working state in some organisms at this time are those related to air breathing to locomotion and to food intake If such reaction patterns are to be operative, external and internal receptor mechanisms must be sufficiently matured to allow adaptive behavior to be initiated by changes in the environment encountered by the organism immediately after birth The nervous system, including both peripheral and central mechanisms, must to some degree be ready to mediate response Necessary motor systems must be functional The fact that organisms are born at very different levels of general morphological development therefore is important for one who would discuss the phylogenetic relationships of fetal behavioral growth

The opossum with a gestation period of twelve and three quarter days in many respects is born as a relatively early fetus (13) But it must be noted that this organism does at this early stage have necessary mechanism for locomotion air breathing and food intake By their own efforts and without assistance from the mother these young organisms in [illegible] nourish themselves by taking milk through their still primitive mouths The opossum does not have an elaborate placenta and of all the mammals they remain the shortest time in the uterus As shown by Langworthy the opossum brain and peripheral nervous system is the most primitive of any known in newborn mammals (14)

The guinea pig on the other hand except in size is born in almost adult form Its gestation period of about nine weeks compared with the relatively few days of growth before birth of the opossum presents many points of differences between these two types of fetal life (15) The adult guinea pig and the adult opossum have different modes of life It would be hard to say however which of these species is more effectively adapted to its total

were, to receive their natural cue to come onto the stage and perform their full function. The ontogenetic study of the air righting reflex in such animals as cats and rabbits, for example, illustrates this generalization (8).

Another generalization which the present author believes experimental work on a wide variety of fetal types has established with some assurance is that of the relative *specificity of response to precise stimulation* (9). Experiments demonstrate during certain periods of early active fetal life that the responses elicited by particular forms of stimulation, when applied to specific receptors or receptor areas, are relatively invariable. To put this in another way, there is evidence to indicate that as fetal organisms of various species grow they come to have particular cutaneous and other reflexogenous zones that act almost like the pushbuttons of an electric buzzer system, i.e., when touched they release surprisingly specific and unvarying patterns of response. Sometimes these responses are simple and reflex like. At other times they are relatively complex. This generalization, which has been substantiated in much work of the present writer has never, it seems, been sufficiently considered in its full implications for the understanding of fetal and even of adult behavior.

In comparisons of behavior development it is also desirable that as many as possible of the relevant physiological conditions which affect the living organism be taken into consideration and held constant. The work of Sir Joseph Barcroft has shown how many mistakes were made in this field before the importance was recognized of the availability of oxygen for the central nervous system at various stages in fetal growth (10). Jasper, Bridgman and the present writer have shown in this connection that by tying off the umbilical cord of late fetal guinea pigs an immediate effect on the recorded electrical activity of the higher brain centers may be demonstrated (11). Such reduction in oxygen content of the blood does not for a time abolish but rather augments lower reflex activity of the already dying fetus. This observation emphasizes the fact that control of the conditions affecting the oxygen intake of fetal organisms, anesthetics that have been given to the maternal organisms, general blood supply, temperature, external stimulation such as the effect of gravity, and the like, is most important for one who would make observations on early mammalian behavior which are to be verified. Real knowledge of the internal as well as the external environment of the developing fetus is thus as important for one who would describe early development as it is for the physiologist who is concerned with changes in the behavior of normal adult human beings under varying external conditions, such as alteration in altitude.

Similarities and differences of basic conditions of biological development are also important for one who would consider and compare the phylogeny of behavior patterns. *The differences in onset and development of behavior*

upon whom the scale was standardized. While a procedure of this sort presents difficulties when individuals of the same species but of different chronological age are compared, these difficulties can be dealt with by appropriate statistical procedures.

When comparisons between species rather than between individuals are attempted in a similar manner, however, new difficulties present themselves. Here one is concerned not only with a behavioral factor involving the relation of the so-called mental age to chronological age, but also with organisms that develop at different rates and in the end arrive at different levels of capacity. In spite of this fact a detailed scale of this sort seems to present the only really promising lead for the effective comparison of behavior in various species during fetal life.

The pitfalls in this attempt are like those which have long beset comparative psychologists. Learning curves can be drawn to describe habit acquisition in porpoises, bats, and lions. But it is not easy to be sure that the tasks presented to these three species of organisms are such that they can be equally well performed by all of them and thus allow any easy quantitative comparison between them in basic learning ability. In animal psychology efforts have been made from time to time to set up standard experimental situations for use in learning experiments on frogs, birds, lizards, rats, cats, monkeys, chimpanzees, men, and other organisms. Unfortunately, in such series the intrinsic, inborn, or natural *patterns of behavior*, especially as related to motivation, are so diverse that quantitative comparison between the adaptive responses elicited, even on objectively identical problems, is all but impossible.

This same difficulty is present in all comparisons of the development of behavior patterns. This means that the full course of growth of response from its so-called ontogenetic zero to adult life must first be fully described in each species to be compared. Whenever possible the stimuli used in this work should be quantified. For example, if the onset and development of response of tactile stimulation are to be considered, it is important that the pressures exerted by the esthesiometers used should in all cases be known and recorded (16). This same requirement applies to the photic stimulation of the eye, the sound stimulation to the ear, temperature stimulation, and indeed to all other external patterns of energy applied to the specific receptors of developing organisms.

In addition, statements about behavior growth ...
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... the present writer set themselves the problem of determining the time of onset and the character of the earliest responses of the fetal guinea pig (17). The insemination time

environment It may be noted, for instance, that in sensory capacity and motor skill and in many other respects the newborn guinea pig and indeed the late fetal guinea pig is an effective organism Almost every writer on guinea pigs has at some time spoken of it as a Minerva like organism born like that goddess, ready for immediate effective action From the point of view of biological adaptation this means that the newborn guinea pig can run with a group of adult organisms of the same species without too much difficulty, and is thus ready for quick terrestrial migrations that may well have been necessary for the preservation of the life of its running ancestors The pouch young opossum on the other hand is well protected and is carried by its mother as she moves through tree branches Thus comparable biological problems have been solved by different means These two different evolutionary answers to this problem are it seems related to two very different patterns of fetal behavioral growth

If we continue to think of the opossum and the guinea pig it is clear that counting of the number of days from insemination therefore gives a most unsatisfactory base line for behavior comparison The same problem must be faced in comparing many other species

In similar manner a stretching out by statistical means of the total period of prenatal development so that phylogenetic comparison is made not in absolute units of time but in percent of the total developmental period from fertilization to birth is also not satisfactory This procedure of using percentages of total fetal growth period is inappropriate because as has been pointed out certain behavior mechanisms must be ready for effective operation when parturition takes place although other mechanisms may remain in what would be in another species an early fetal condition

The author of the present paper has attempted to work out a functional behavior scale that might be used for comparative purposes from species to species during early development This attempt however is still most preliminary The notion behind this endeavor is similar to that which has been used in comparing individual human abilities on mental age scales

In the famous Binet Simon test for example human individuals of the same chronological age are presented with standard situations which evoke known types of response Since the reactions elicited are not always the same in children of identical chronological age it is possible after establishing standard batteries of problems and test situations to determine average performances on these sets of problems at any given age and by the use of statistical procedures to arrive at or define the expected norms of behavior for particular chronological ages When an age scale of this sort has been constructed it is possible to test new individuals on the now standard

havioral or mental maturity

with the series of individuals

own work, I have found that rats during development, will react under experimental conditions long before they really should. They are not completely structurally developed to the place where they should react under normal conditions but they do under experimental ones. In other words we can elicit a response experimentally which would normally not take place for a considerable period of time and for which the mechanism is not completely prepared. When you begin to study the muscular system you find that before any striations are present the normal irritability of the muscle is sufficient to set up on the fourteenth day, areas which can be caused to contract by direct stimulation of the muscle.

Secondly I would like to consider that if one experimentally creates a partial but continuous anoxia the organism is getting a very low blood supply during its crucial period of nervous system development. This experiment can be done in the rat since it has two mechanisms by which it gets its nutrition one coming through the yolk sac placenta and the other through the discoid placenta. One can work with either one of these at definite times before the nervous system is formed securing complete differentiation of the nervous system but inhibiting its growth. In other words, anoxia if produced very gradually and not suddenly as in the case which Dr Carmichael reports will not cause the same sort of result. I think Dr Windle would probably bear that out too in the course of some of his experiments.

The phylogeny of behavior then is something which when you look at the individual does not fit into a pattern because of the various accessory ways in which it is being approached and in which it is being controlled. I think that Dr Carmichael has done a very valuable service in pointing out the complexity of the problem, the interrelations which will have to be studied and the conditions under which the experimentation will have to take place.

DR. K. S. LASHLEY (Orange Park, Florida): When comparing the brains and the behavior of animals at different levels in the phylogenetic scale I have been much puzzled by the lack [illegible]

[illegible] at about the same rate. They show the same types of perceptual generalization the differentiation of [illegible]

[illegible] organization of nerve cells and are largely independent of the gross structures which have been evolved in phylogenet[illegible]

[illegible]

DR. LEONARD C[illegible]

com[illegible]

of a large number of maternal organisms was accurately determined. Then some 47 fetal litters were studied at about the age when behavior was expected to begin. On the basis of this study it was possible to state with some statistical assurance that the first response of the fetal guinea pig begins in the last hours of the twenty fifth day after insemination. It was also possible on the basis of this study to show that the first reaction of the guinea pig fetus is a movement of the head and of the foreleg.

Whenever possible in the study of phylogenetic development of behavior patterns a comparison of several methods of recording activity is advisable. An example may make this statement more clear. Rawdon Smith, Wellman and the present writer have demonstrated in the unborn guinea pig by electrophysiological as well as behavioral methods the time of the onset of the functional effectiveness of the fetal ear to airborn stimulus energies or sounds. It was demonstrated that the first appearance of the electrical cochlear effect which could be amplified and recorded came at 52 post insemination days (18). At just the same number of post insemination days study had shown that it was possible to elicit externally observable responses to airborn stimuli (8). This mutual confirmation by two methods is scientifically satisfying in an area in which there are many variables.

In the study and comparison of the phylogenetic development of behavior patterns it thus appears that there is no royal road to knowledge. On the contrary, a cumulative study of behavior development under known conditions in each species is still the only sure approach in this area. Gradually total behavior inventories of organisms that are to be compared are being built up. Thus, those interested in comparing the growth of behavior from species to species may do so for specific responses by comparing items in such total records.

A knowledge of the phylogenetic development of behavior patterns has much significance for neurology and the behavioral sciences, but it is an area of investigation in which sound conclusions should be based on a great deal of exacting scientific work.

DISCUSSION

DR J S NICHOLAS [New Haven, Conn] Mr Chairman, there are a few points in this very interesting discussion which Dr Carmichael has presented which I would like to take up, more or less from the embryonal viewpoint.

The adoption of the phylogenetic viewpoint certainly has some interesting connotations for the student of behavior. The adoption of the phylogenetic viewpoint in behavior from the standpoint of cultural civilization is certainly a very important one, not because it is so significant but because it gives us a new interrelationship to look at, one which makes us realize, I think, the vagaries and the questions which are bound to come up in the course of the analysis of behavior.

To get down to specific things first, I would like to know something about the pushbutton that brings these behavior patterns in, especially reflexogenous zones. In the course of my

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ake
ne In oth r word we can el ct a response experim e tal w t w a ake place for a co id rabl period of t e a d fr wl ch the mechan sn n t c pletely pre pared Wler you begin to study tle m scular s te you f d that fat r a s strat s are prese t the normal irritabil ty of tle muscle is s ff ent to set up o tle f urter th lss

n rvou s tem le elop t Tl s experime t c be do e n tle rat s e it l as tw n sel am n l wh l t g ts its utrit on o e com g tl rough the y lk sac place ta and the other through the d scoid placenta O e can w rk with e ther one of these at defi te t mes but re tle nervous s tem for and securing e c plete l fferent t of the nervous s te n lut at ut g t grout I otler word an x if produced ery gr fu lly a l t t a l lent a the case wl l Dr Carm hael rep rts w ll not ee se tle sa e sort of re ult I th nk Dr W ndle would probably bear that out too, n the course of some of l s experiments

The pl logeny of behs or then is someth ng wl l wl en y u look at the ind vidual does not fit nto a p tt rn because of the various nerv or ways in wl l t is be ng ap proa hed and n which t is be ng controlled I th nk tl at Dr Carm ichael has I ne a very aluable service in po nt ng out tle complex t of the problem the nterreactions which w ll ha e to be studied and the cond t on under wl ch the experi e tat on will ha e to take place

Dr K S L ley (O ange P k Flor d) Wl e co mpa g the bra ns a d the beha ior of an mal at d ffer nt le el th phylogen t c scale W

u la e they s ow the sa e t p f percept al ge era zat on tle d ffere t at o of figure from ground the recogn t on of s l lar t es a g objec All s ow m l r perception of spat al relat ons There are e en sugge t s f g t or a prim t e gra p of log al rel t ons, by an a al a prim t e as the artl ropod The d f erences are q ant t e rather than qualitat e

It looks a though these ba mechan ms of b l a ior are so n ture of tle nerve of the gross stru n rvous e n se o t ng the le na l of the n t and of re ers b v of what I s o ce ler tarted The prim t e mammal was almost erta nocturnal making l tle u e of v n T m eloped a n ts te ect op l a

My po n acing of the structural cl a ges of tle bra n s o v ior important for understan i g of the e olut on of tle bra n the gross stru t ral changes may be almo t completely rrele ant to tle problem of the e olution of beha ral o mental tra ts

Dr Leon rd C rm c el (Cl ing T me w ll not allow me t tr to a swer all of the co mments of the d t ngu hed members f tle Com m on

Ant pitory maturat on about which Dr Nichola spoke s nteres t g One sat fact ry

aspect of this problem is that in certain ways one may quantify such development For example, if the function of the eye is under consideration, one may measure some visual functions long before the eye is typically called upon to do any seeing The amount and pattern of light energy that is required to bring about a measureable response on stimulating the fetal eye can be determined at a series of ages This can also be done in other senses In such processes one can measure back from the time when, in the normal animal the function is first called upon to play a useful part in the economy of the organism to the true zero point of activity in each process in question

A second point concerned the specificity of response This could be considered at great length Some years ago I studied upwards of 100 litters of fetal guinea pigs of known insemination age As each maternal organism was ready, each fetus of the litter was studied and protocols were dictated and typed This whole study required many months In each fetus studied the same reflexogenous areas were stimulated with quantified stimuli When the protocols were finally studied an unexpected result appeared When all the series of organisms were considered it bec
followed stimulation of each of the
were a pushbutton attached to a sp
most of active fetal life It seems to me that it is a rather interesting finding Of course especially in late fetal life, the responses were sometimes relatively complicated but often too they were quite specific and reflex like I do not want to suggest that this observation settles the general question of individuation versus integration but rather to indicate that with minimal quantified tactile stimulation of known reflexogenous zones the organism responds in a surprisingly constant way during quite a long developmental period

Then turning to Dr Lashley's statement I wish I really had time to make some comment upon the similarities that he has so well pointed out in a variety of organisms My experience with a much more limited group of mammals certainly bears out his statement

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CHAPTER VIII

EARLY HUMAN FETAL BEHAVIOR, WITH A PRELIMINARY NOTE ON DOUBLE SIMULTANEOUS FETAL STIMULATION

DAVENPORT HOOKER[1]

INTRODUCTION

In the normally developing organism, behavior is an expression of inherited structure. During prenatal life in mammals, including man, reflex activity, whether proprioceptive, exteroceptive, or so called spontaneous activity (now generally recognized as reflex in nature) constitutes the major manifestation of developing behavior. As the normal individual grows older and voluntary activities are exhibited, the environmental factors of postnatal life modify behavior, although the basic potentialities of the organism are still predicated upon inherited structure. It is well known that the maternal diet or certain diseases suffered by the mother may prenatally alter structure (cf. 22, 23). Where these early changes in structure seriously affect the neuromuscular mechanism, alterations in behavior may be expected.

In the following discussion, only two aspects of the reflex behavior of normal human embryos and early fetuses will be presented. These have been selected because they illustrate inherited structural basis in relation to activity. They are: 1) responses to exteroceptive stimulation in the cutaneous areas supplied by the trigeminal nerve, and 2) the results so far secured from double simultaneous homolateral stimulation of face and hand and of hand and foot. For a discussion of other aspects of the development of human fetal behavior and for additional pertinent literature and references, Gesell (13), Hooker (16), Minkowski (21) and Windle (25) may be consulted.

[1] From the Department of Anatomy, University of Pittsburgh School of Medicine, Pittsburgh, Pa. The physiological and morphological studies on human prenatal development of which this is publication no. 23 have been aided by grants from the Penrose Fund of the [illegible] N[illegible] York, from the Un[illegible] Pittsburgh, and from U. S. Departm[illegible]nt of

RESPONSES TO TRIGEMINAL STIMULATION

It has long been established (1, 3, 16 21) that the cutaneous sensory nerve first to become functional in the mammals is the trigeminal nerve However the order in which the three divisions of V become sensitive to exteroceptive stimuli as shown by the eliciting of reflexes, appears to vary in different forms In man stimulation of the perioral integument, supplied by the maxillary and mandibular divisions of the trigeminal nerve, causes reflex responses to stimulation before that of skin innervated by the ophthalmic division (14, 15, 16 17) In fact stimulation of the perioral integument may elicit reflex responses by about 7½ weeks of menstrual age* Furthermore until the fetus has reached approximately 10 weeks of age, the perioral region is the only cutaneous area over the entire fetal body which is sensitive to exteroceptive stimuli

It should be emphasized that the reflexogenic perioral region is much more restricted at first than the adult distribution of the maxillary and mandibular divisions of V might indicate Only the region about the lips and nasal alae give reflex responses to exteroceptive stimuli at 7½ weeks

By 9½ weeks the reflexogenic cutaneous area has spread over most of the nose the chin and the cheeks closely adjacent to the mouth By 10 to 10½ weeks the upper eyelids are reflexogenic in the majority of fetuses The sides back and top of the head do not become reflexogenic during fetal life

The responses to be elicited from the embryonic and fetal integument supplied by the trigeminal nerve belong in two categories 1) *generalized* reactions of the organism as a whole produced chiefly by the axial musculature and 2) local responses The axial reflexes which, as noted, first appear at about 7½ weeks are at their inception, restricted to the muscles of the neck but later expand caudally ultimately to involve all of the trunk and limb girdle musculature The extent and character of these axial responses are so typical of the age level of the individual under observation that it has been possible to assign the correct age to embryos and younger fetuses on the basis of the nature of their reflexes alone Precocity or backwardness in performance are almost *never found* in fetuses of less than 11 weeks After that age an increasing variability in the level of performance of different individuals of the same age becomes evident

At 7½ weeks exteroceptive stimulation with a fine hair over the *perioral* sensitive cutaneous area causes a contralateral flexion of the neck Ipsilateral responses do occur at slightly older ages but are rare and none has been seen at 7½ weeks This earliest response has been reported by Fitzgerald and Windle (12) and by Hooker (15 16)

* All ages given in this paper are based on actual or estimated menstrual age

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which opens the mouth is effected certainly by the suprahyoid and possibly by the infrahyoid muscles (see 18) The subsequent closure of the mouth is a slow relaxation of the muscles which opened it Mouth closure is thus not an active reflex at this age

The second local response to appear has been observed once only, at 10½ weeks Stimulation of the perioral region caused deglutition Swallowing has been a quite constant finding from 12½ weeks on, especially to repeated perioral stimulation, or to touching the inside of the mouth

The earliest local reflex to involve the facial muscles occurs at 10 to 10½ weeks Occasionally at this age, when the upper eyelid is gently stroked, a contraction of the orbicularis oculi muscle is elicited This becomes a constantly evoked reflex by 12 to 13 weeks Similarly, beginning at 11 weeks occasional homolateral contraction of the corrugator supercilii muscle has been observed to follow upper eyelid stimulation By 13 weeks, corrugator contraction usually through not always accompanies orbicularis contraction on stimulation of the upper eyelid Thus, orbicular contraction is the first reflex manifestation of function in the ophthalmic division of the trigeminal to appear and with corrugator activity remains almost the only activity excited by cutaneous stimulation of that division of V throughout fetal life It is thus evident that functioning of the ophthalmic division as judged by the reflexes which can be elicited does not begin in the human fetus until some two and a half weeks after the onset of excitability in the areas supplied by the other two divisions of V No corneal reflexes have been tested, of course as the eyelids fuse in the 9th week in human fetuses do not reopen until after the 25th week and are not opened spontaneously before birth

Other local responses to trigeminal stimulation which involve facial muscles are largely limited to the mouth and nose, both as to the reflexogenous area eliciting them (maxillary and mandibular divisions of V) and as to the site of the effector muscles An exception is contraction of the orbicularis oculi muscle observed at 13 weeks in response to upper lip stimulation In the few cases in which this reflex response was observed, the scowling (contraction of the corrugator supercilii muscle) seen earlier to accompany eyelid squinting was absent insofar as could be determined

Light stimulation of the rima oris at about 12½ weeks may elicit a firm closure of the lips which is momentary in the slightly less well developed individuals of the age group but becomes maintained in fetuses somewhat more advanced in development or a few days older When stimulation of the rima oris is repeated at this age swallowing often ensues as it did at 10½ weeks to maxillo mandibular area stimulation

By 8 weeks the neuromuscular mechanism has developed in a caudal direction sufficiently to involve the upper trunk muscles in the response. The shoulder girdle muscles may also begin to exhibit slight activity with the result that the brachia may quiver throughout their length as the axial flexion spreads to include the upper trunk region.

At 8½ weeks, exteroceptive stimulation in the perioral region causes primarily a contralateral flexion of the neck and trunk accompanied by extension of both brachia at the shoulders and a slight rotation of the pelvis turning the symphysis pubis away from the side of the axial flexion. Involvement of the lower trunk is less marked at this age than it is by 9½ weeks when all components of this response become more complete.

At about the age of 10½ weeks axial extension begins to replace lateral flexion, the two types of response being intermixed at first, extension gradually replacing lateral flexion by 11 to 12 weeks of age. However, toward the end of the observations on an individual exhibiting only axial extension at first, there is a tendency for a return of the lateral axial flexion response. Fatigue may be a contributing factor to this regression to an earlier type of response, but there is no proof of this. Efforts to avoid anoxia and asphyxia of the fetuses during observation have so far failed. Although there is reason to believe that anoxia and asphyxia do not affect the essential character of reflexes while they are elicitable (18), either or both halt all reflexes after a time. However, there is much evidence to indicate that more recently appearing reflexes succumb more readily to anoxemia *than do those which are older and well established (see 2 and p. 105).*

As axial extension becomes the constant response to exteroceptive stimulation in the perioral region at 11 to 12 weeks, pelvic rotation fades. When lateral axial flexion returns as a regressive type of response under the influence of anoxia and asphyxia, pelvic rotation tends to reappear with it. With the progressive rise of axial extension, the lateral flexion of the neck disappears to be replaced by neck rotation which results in turning the face away from the stimulus. The axial extension type of reflex in response to stimulation over the sensitive cutaneous area supplied by the maxillary and mandibular divisions of the trigeminal persists often into the thirteenth or fourteenth week. Axial responses continue to be manifested under certain conditions throughout much of fetal life, but they cease to be the predominant feature of the reflex response between 13 and 13½ weeks of age. In that period, local responses to trigeminal stimulation, which first appear at about 9½ weeks of age, gradually supersede total body responses

the trigeminal area of distribu

ng stimulation over the edge of

the lower lip The re ugh incomplete opening of the mouth. Careful observation indicates that the active mandibular depression

mislocated Normal adults and those with schizophrenia or aphasia however perceive both stimuli and correctly locate them after relatively few initial errors although more errors are made by the patients than by normal adults Cohn termed the persistent selection of the more cephalic stimulus site over the more distal as *rostral dominance* Bender and his associates do not agree that dominance is always rostral because they found that the foot was dominant over the hand Hence they prefer to speak of extinction of one percept

Fink and Bender (10) believe that the pattern of dominance shown by their tests may be an inherent function of the organism If this be true and it may well be correct double simultaneous stimulation tests on fetuses should provide evidence indicating to what extent the pattern *is inherent* and dependent upon the inherited structure free from any effects of learning Bender and his associates maintain that their tests are perceptual If by *this they imply that* the responses are mediated at a cortical level of central nervous system function further inquiry may be necessary as they employed relatively crude general tactual and pain stimuli Naturally the *tests made on fetuses* to be presented here are on a purely reflex level Nevertheless inasmuch as the inherent *patterns of higher nervous system* centers are based on those of the lower centers (8 9) any *pattern of dominance* that might be seen in the fetus should indicate what aspects of the postnatal dominance pattern are actually *inherited by the individual* Furthermore it would appear that Cohn s (6) observations on extinction of the Babinski reflex in patients with hemiplegia indicate that under certain abnormal conditions as *lesions involving* the pyramidal tracts extinction may occur on a reflex level in the adult as well as in the fetus

Fortunately for the purpose of testing fetal dominance characteristic reflexes are elicited by facial palmar and plantar stimulation The reflexes elicited by facial (trigeminal) stimulation have been presented

The first reflex involving receptors associated with spinal nerves in the human fetus appears by about 10½ weeks in response to stimulation in the palm of the hand At that time the fingers of the hand stimulated flex incompletely the thumb rarely participating Later this partial finger closure is often accompanied by *wrist flexion* and so ... flexion

(1o) He

a respon ... has been secured

In more advanced fetuses of 10½ weeks and in all at 11½ weeks stimulation of the sole of the *foot causes* toe movement In the youngest fetuses exhibiting toe movement the *response is practically* always plantar flexion By 11½ weeks toe movements on stimulation of the foot sole may be either plantar flexion of all toes or dorsiflexion of the hallux and fanning

stimulation on either side in the area between the upper lip, cheek and nose evokes a contraction of the quadratus labii superioris muscle producing a sneering expression. The face is rotated away from the stimulus. This quadratus contraction follows stimulation by lightly stroking the region with a fine hair. In evoking systemic reflexes, where the response is at a distance from the area stimulated, the use of stiffer aesthesiometers is not contraindicated. However, in eliciting local reflexes it is essential that any possibility of direct mechanical stimulation of the muscles be avoided.

By 14 weeks, and perhaps earlier, stimulation of the tip of the tongue causes its withdrawal and, when repeated, deglutition. It is unusual to find the early fetal mouth open for a long enough period to test tongue reflexes. Separation of the lips by the investigator merely results in lip reflexes. Hence, tongue stimulation has been rare in these observations. Similarly, stimulation of the inside of the cheek has been carried out in only a very few cases between 11 and 14 weeks. Swallowing has been the only reflex so elicited.

No new reflexes following stimulation of the trigeminal areas have been observed after 14 weeks, except for the development of the suctorial reflex, which is a complex activity involving, when perfected, a number of different muscle groups. However, this reflex is at first limited to the lips and follows a definite sequence of responses according to age. From 12½ to approximately 17 weeks, stimulation of either lip causes lip closure. At about 17 weeks, stimulation of the upper lip causes its protrusion, while that of the lower lip brings about its upward movement, thus closing it against the upper lip. At about 20 weeks, both lips protrude when their respective mucous membranes are touched, either separately or together. By 22 weeks, both lips are not only protruded but pursed. The number of cases observed in this age range is not sufficient for exact determination of the specific age at which actual sucking responses begin, but it has been observed as an active and audible procedure at 29 weeks. Insofar as the Pittsburgh studies have gone, the development of the suctorial response completes the sequence of activities initiated by stimulation of the cutaneous area supplied by the trigeminal nerve.

DOUBLE SIMULTANEOUS FETAL STIMULATION

Recently, Cohn (7) and Bender and his associates (4, 10, 11) have used two stimuli simultaneously applied to various cutaneous areas of the body, homolaterally or heterolaterally, as a test of perceptive ability. Their results are of considerable interest because, with young children (7, 10) and with adult patients having brain damage (11), one of the two stimuli, often that more distally located on the body, either is not perceived or is

mislocated Normal adults and those with schizophrenia or aphasia, however perceive both stimuli and correctly locate them after relatively few initial errors although more errors are made by the patients than by normal adults Cohn termed the persistent selection of the more cephalic stimulus site over the more distal as 'rostral dominance' Bender and his associates do not agree that dominance is always rostral because they found that the foot was dominant over the hand Hence, they prefer to speak of 'extinction of one percept

Fink and Bender (10) believe that 'the pattern of dominance' shown by their tests may be 'an inherent function of the organism' If this be true and it may well be correct double simultaneous stimulation tests on fetuses should provide evidence indicating to what extent the pattern is inherent and dependent upon the inherited structure, free from any effects of learning Bender and his associates maintain that their tests are perceptual If by this they imply that the responses are mediated at a cortical level of central nervous system function further inquiry may be necessary, *as they* employed relatively crude general tactual and pain stimuli Naturally the *tests made* on fetuses to be presented here are on a purely reflex level Nevertheless inasmuch as the inherent patterns of higher nervous system centers are based on those of the lower centers (8 9) any pattern of dominance that might be seen in the fetus should indicate what aspects of the postnatal dominance pattern are actually inherited by the individual Furthermore it would appear that Cohn s (6) observations on extinction of the Babinski *reflex in* patients with hemiplegia indicate that under certain abn[illegible]

tinction n[illegible]

Fortuna[illegible] of testing fetal dominance characteristic reflexes are elicited by facial palmar and plantar stimulation The reflexes elicited by *facial (trigeminal)* stimulation have been presented

The first reflex involving *receptors* associated with spinal nerves in the human fetus appears by about $10\frac{1}{2}$ weeks in response to [illegible] the [illegible]

in[illegible]

el[illegible] wrist flexion and sometimes by elbow flexion forearm pronation and *rotation* of the brachium at the shoulder (15) However partial finger closure alone is adequate to demonstrate that a response to palmar stimulation has been secured

In more advanced fetuses of $10\frac{1}{2}$ weeks and in all at $11\frac{1}{2}$ weeks stimulation of the sole of the foot causes toe movement In the youngest fetuses exhibiting toe movement the response is practically always plantar flexion By $11\frac{1}{2}$ weeks toe movements on stimulation of the foot sole may be either plantar flexion of all *toes* or dorsiflexion of the hallux and fanning

of the other toes One or the other response may predominate, or both may be intermingled, from 11½ to about 14 weeks By 14 weeks, dorsiflexion of the hallux and toe fanning is the principal response evoked by foot sole stimulation and continues as the characteristic plantar reflex throughout the remainder of fetal life

These typical reflex responses to stimulation of the face, of the palm, or of the sole of the foot are thus available to test the reactions to double simultaneous stimulation of face and hand or of hand and foot Perioral stimulation causes contralateral trunk flexion up to about 13 or 14 weeks Thereafter local responses predominate Palmar stimulation evokes partial finger flexion and plantar stimulation causes toe movements

During the past year, three human fetuses of 10½, 13 and 13½ weeks of age have been tested with double simultaneous homolateral stimulation In the 10½ and 13 weeks fetuses, face and palm areas were simultaneously tested In the 13 and 13½ weeks fetuses, palm and foot sole were stimulated simultaneously The results are shown in tables 11 and 12

Reference to table 11 will demonstrate a satisfactory test sequence in the case of the 10½ weeks fetus Typical responses to single stimulation of palm and of face, carried out separately before and after the two double simultaneous stimulations of palm and face, validate the results, in that they demonstrate both reflex arcs to be functional, independently, at each of these times Hence, these arcs were functional when the double simultaneous tests were made The dominance of face over hand, or the extinction, or the inhibition of the hand responses whichever one prefers to call it, in the two simultaneous stimulations of face and hand was therefore not caused by anoxic disturbance to the palmar arc

TABLE 11

Tests with double simultaneous stimulation of face and hand on human fetuses

Age	Stimulation	Response
10½ wks M A #136	1) Single of right palm	Partial finger closure
	2) Single of right perioral area	Contralateral trunk flexion
	3) *Double simult rt face & hand*	*Contralateral trunk flexion only*
	4) *Double simult rt face & hand*	*Contralateral trunk flexion only*
	5) Single of right palm	Partial finger closure
	6) Single of right upper lip	Contralateral trunk flexion
13 wks M A #138	1) Single of right lower lip	Contralateral trunk flexion
	2) Single of right palm	Partial finger closure
	3) *Double simult rt face & hand*	*Contralateral trunk flexion, only*
	4) Single of right perioral area	Contralateral trunk flexion
	5) Single of right palm	No response

TABLE 12

Tests with double simultaneous stimulation of hand and foot on human fetuses

Age	Stimulation	Response
(1)	1) Single of right sole	Plantar flexion of toes
13 wks	2) Single of right palm	Partial finger flexion
M A	3) *Double simult rt palm & sole*	*Partial finger flexion, only*
#138	4) Single of right sole	Plantar toe flexion
	5) Single of right palm	Partial finger flexion
	6) *Double simult rt palm & sole*	*Partial finger flexion only*
	7) *Double simult rt palm & sole*	*Partial finger flexion only*
	8) Single of right palm	Partial finger flexion
	9) Single of right sole	Plantar toe flexion
(2)	1) Single of left sole	Plantar toe flexion
13 wks	2) Single of left palm	Partial finger flexion
M A	3) *Double simult left palm & sole*	*Partial finger flexion only*
#138	4) *Double simult left palm & sole*	*Partial finger flexion, only*
	5) Single of left palm	Partial finger flexion
	6) Single of left sole	No response
	1) Single of right palm	Partial finger closure
13½ wks	2) Single of right sole	Plantar toe flexion
M A	3) Single of right sole	Plantar toe flexion
#137	4) Single of right palm followed at once by single of right sole	Partial finger flexion followed at once by plantar toe flexion
	5) Single of right sole	Plantar toe flexion
	6) *Double simult rt palm & sole*	*Partial finger flexion only*
	7) *Double simult rt palm & sole*	*Partial finger flexion only*
	8) Single of right sole	Plantar toe flexion
	9) Single of right palm (later)	Partial finger closure

Unfortunately the face hand test on the 13 weeks fetus is not similarly validated because no *response* to stimulation of the palm alone was secured following the double simultaneous stimulation of [illegible] Hence [illegible] b [illegible] n [illegible] may have been in fact functional, no proof can be offered that stimulation of the pal[illegible] finger[illegible] fet[illegible] by the progressive anoxia and asphyxia which it is undergoing As has been [illegible] there is [illegible] its nat[illegible] progre[illegible] capacity

of the fetus to respond to any exteroceptive stimulus. Those reflexes which are the more recent in appearance are the first to disappear (see also Angulo 2) as is demonstrated by the fact that the 13 weeks fetus had been used for a series of hand foot tests (table 12) before the face hand test in table 11 was made. Thus after the sole of the foot no longer responded to stimulation the palmar reflex could still be evoked but its reflexogenic capacity disappeared before that of the area receiving distribution from the maxillary mandibular division of V. Developmentally, the reflexes appear in the reverse order of their extinction by anoxia.

Table 12 presents the tests so far made with double simultaneous homolateral stimulation of palm and sole in two fetuses, one of 13 weeks, the other of $13\frac{1}{2}$ weeks. Three double simultaneous stimulations of the palm and sole on the right side of the 13 weeks fetus were made, with a single stimulation of each of the two cutaneous areas evoking their appropriate responses at the beginning, after the first two double stimulations and again at the end of the third double simultaneous stimulation. The first three simultaneous stimulations with this fetus are thus *adequately* validated. The uniform suppression of the plantar reflexes in each of these three double simultaneous stimulations of palm and sole can, therefore, be considered to be of some significance.

The second test sequence on the 13 weeks fetus (table 12) is not substantiated, however, as the last single stimulation of the sole of the foot failed to evoke a response. Thus it cannot be proved that the plantar reflex could have been obtained at the time of the double simultaneous stimulations on this fetus had the sole alone been tested.

The two simultaneous stimulations of palm and sole carried out on the $13\frac{1}{2}$ weeks fetus are, however, also well authenticated. A plantar reflex was secured after the double stimulation tests. Furthermore, even though the last palmar stimulation followed two intervening stimulations elsewhere on the body, both reflex arcs were functional at the time of the double stimulation tests. Consequently, a total of five acceptable hand foot tests are available from the 13 and $13\frac{1}{2}$ weeks fetuses.

Admittedly, the evidence from the observations on double simultaneous homolateral stimulation of face and hand or of hand and foot is limited as yet. Nevertheless, properly validated tests are available in each category with results which are uniform for each type of double simultaneous stimulation. Many more tests of both kinds are needed before more than tentative conclusions can be drawn. It has been observed in work with human fetuses that the age at which a particular response first appears may often have to be revised to a younger age, especially when the reflex can be sought nearer the beginning of the observations on the individual fetus. However, as far as our results indicate, the kind of activity exhibited consistently following

a given stimulus remains relatively unchanged in subsequent tests The results secured from these few face hand and hand foot tests are clearly consistent It would appear therefore that at least a trend has been established This trend, though awaiting additional evidence before definite conclusions can be drawn can nonetheless be discussed as to its possible implications

As has already been noted Cohn (7), working with children from 3 to 10 years old was impressed by his findings that the more rostral of two homolateral stimuli applied simultaneously, one to a more proximal part of the body, one to a more distal, such as face and hand, was the one most often perceived by young children By 6 years however, normal children should correctly perceive and locate both stimuli If, under these test conditions rostral dominance persisted beyond 6 years of age Cohn believes the subject may be presumed to be mentally retarded *He concluded that sentiency to, and the resolution of, multiple disparate cutaneous stimuli is a learned process* (p 122)

The evidence furnished by these preliminary double simultaneous stimulation tests on fetuses suggests that rostral dominance may be exhibited in fetal life as soon as two different cutaneous areas become reflexogenic It would further appear, from the observations made thus far that the basis for dominance in the fetus (and possibly in the infant and very young child) may be the time sequence factor i e, *the dominant area of response to double simultaneous stimulation in each case is probably that to appear first in development* The fetal results lend further credence, if such be necessary, to the statement of Cohn (7) that *the ability to perceive and distinguish the locations of two stimuli in older children and normal adults is indeed a learned process*

The fetal dominance *of hand over foot* is at variance with the results of Fink and Bender (10) who report that the foot is dominant over the hand in a l lt hem l

the

chi u s u served They report that foot dominance over hand was evident in 51 *per cent of the* 101 tests made on children, and that the data are consistent throughout the entire age group[2]

Bender (4) defines double simultaneous stimulation as two discrete stimuli applied synchronously *or in close succession in different parts* of the sensory field (p 7) In regard to the effectiveness of two *stimuli* applied in close *succession in fetuses* however, attention is directed to table 12 stimulation and response *no* 4 of the 13½ weeks fetus These stimulations were intended to be simultaneous but a difference in the time

[2] Personal communication from Morris B Bender M D

of the fetus to respond to any exteroceptive stimulus Those reflexes which are the more recent in appearance are the first to disappear (see also, Angulo, 2) as is demonstrated by the fact that the 13 weeks fetus had been used for a series of hand-foot tests (table 12) before the face hand test in table 11 was made. Thus, after the sole of the foot no longer responded to stimulation, the palmar reflex could still be evoked, but its reflexogenic capacity disappeared before that of the area receiving distribution from the maxillary-mandibular division of V Developmentally, these reflexes appear in the reverse order of their extinction by anoxia

Table 12 presents the tests so far made with double simultaneous homolateral stimulation of palm and sole in two fetuses, one of 13 weeks, the other of 13½ weeks Three double simultaneous stimulations of the palm and sole on the right side of the 13 weeks fetus were made, with a single stimulation of each of the two cutaneous areas evoking their appropriate responses at the beginning, after the first two double stimulations, and again at the end of the third double simultaneous stimulation The first three simultaneous stimulations with this fetus are thus adequately validated The uniform suppression of the plantar reflexes in each of these three double simultaneous stimulations of palm and sole can, therefore, be considered to be of some significance

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Admittedly, the evidence from the observations on double simultaneous homolateral stimulation of face and hand or of hand and foot is limited, as yet Nevertheless, properly validated tests are available in each category with results which are uniform for each type of double simultaneous stimulation Many more tests of both kinds are needed before more than tentative conclusions can be drawn It has been observed in work with human fetuses that the age at which a particular response first appears may often have to be revised to a younger age, especially when the reflex can be sought nearer the beginning of the observations on the individual fetus However, as far as our results indicate, the kind of activity exhibited consistently following

fetal life but become less predominant with the rise of local reflexes They are manifested chiefly on the side opposite to that stimulated and rarely originate from the area of ophthalmic division distribution The very few cases where they have so originated have been in older fetuses

Structure develops and differentiates in a quite consistent cervicocaudal direction throughout the vertebrate series and is inherent in the inherited pattern of development of that part of the organism Function being dependent upon structural differentiation must therefore also develop in a cervicocaudal manner Hence the caudal spreading of the initial response to exteroceptive stimulation in the region supplied by the maxillary and mandibular divisions of the trigeminal nerve is the functional manifestation of the progressive cervicocaudal development of this portion of the neuromuscular mechanism of the embryo and fetus

An important element of the usual response to unilateral trigeminal stimulation is the movement of the face away from the stimulus This is done in different ways at different ages Initially the face is removed from the stimulus by the contralateral flexion of the neck Later the separation of the face from the stimulus is accomplished by rotation of the head As *Coghill (5)* and others have recognized any activity which causes the embryonic body to move away from a stimulus is an avoiding reaction As the first response to exteroceptive stimulation in the human embryo is thus predominantly an avoiding reaction and as this type of reflex continues to appear during the major portion of fetal life it would appear that developmentally this is the most fundamental response to any external stimulus

Those *responses to* exteroceptive stimulation of the integument supplied by the trigeminal nerve which appear later are local in character They involve facial lingual inframandibular and pharyngeal muscles Responses finding expression in the *facial* muscles are predominantly ipsilateral the others being bilateral Local responses to stimulation of cutaneous areas innervated by the trigeminal nerve make their appearance before the trunk reflexes begin to fade in importance and involve all three divisions of V They gradually *increase in* number and importance while the trunk responses to stimulation in this *region* largely disappear by 13 to 14 weeks except under special circumstances

In the neighborhood of 10 to $10\frac{1}{2}$ weeks skin areas supplied by spinal sensory nerves become reflexogenic to exteroceptive stimulation Prior to that age no purely spinal reflex arcs are functional

The appearance of finger and toe reflexes to exteroceptive stimulation of the palm and sole respectively makes possible an exploration of the effects of double simultaneous stimulation of two points on the body The results of a few preliminary homolateral face hand and hand foot tests indicate a consistent dominance of the more rostral stimulated area over the

of application of the two hairs, though less than a second, was immediately apparent to the investigator and was so dictated at once to the stenographer. This short interval of approximately the same order of magnitude that Bender (4) found not to be perceived by patients, was of sufficient length for the sensory mechanism of the fetus to respond to the two stimuli as separate, so that no suppression of one reflex occurred.

Kingsbury (20)[4] has pointed out that the structures of an embryo differentiate in a cervicocaudal direction, except in the head where growth and differentiation proceed cervicorostrally. In the ontogenetic development of the human individual, it has been demonstrated (16) that activity appears also in a cervicocaudal direction throughout the trunk. This is, of course, to be expected, as function is dependent upon morphological differentiation. The preliminary double simultaneous stimulation tests on fetuses here presented are thus fully in accord with the principle of cervicocaudal morphological differentiation in the body region concerned.

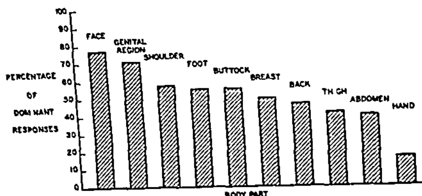
These fetal simultaneous double stimulation tests on hand and foot substantiate Cohn's (7) rostral dominance theory in a *developmental* group much younger than that upon which he based his ideas. It might be that Cohn is correct for very young children, Fink and Bender correct for older children and adults. Furthermore, it may appear that some modifying environmental factor reverses the dominance for older children in the foot-hand tests.

SUMMARY

In the normal sequence of the development of human fetal activity, *the cutaneous areas supplied by the trigeminal nerve mediate* all of the earliest responses to exteroceptive stimulation. Of the three divisions of V, the maxillary and mandibular divisions become reflexogenic before the ophthalmic. The first sensory area is restricted to the region of the lips and nasal alae, constituting a quite limited peri- or circumoral zone. *This limited reflexogenic area expands somewhat with increase in age up to* 9½ or 10 weeks.

The first responses to circumoral stimulation are not local but involve all of the neuromuscular mechanism capable of function. At first limited to the neck muscles, the functional mechanism spreads in a cervicocaudal *direction to include the long trunk muscles and those of the limb girdles.* These trunk muscle responses persist for a relatively long period through

[4] Kingsbury points out in this paper (p. 309) that the law of cephalocaudal differential growth is in part a misnomer. Hence the author prefers the terms cervicocaudal and cervicorostral as having a connotation slightly more in accordance with the sequence noted by Kingsbury.



F g 8 Order of don ıance n nort al cl llren 3 to 6 years of age

In th first place they illustrate the principle of sens ry teract on n t e fetu Seco ll e l ow the nteract on n tle form of a l ck of resp o se to one of the two ap pl ed st mul T l k of re po se that Dr Hooker ol ta e l tle f tus u l r l s co d t ons of test g woul l ten l to el n nate the co cept tl at al l t to perce e one of two t n ul the cl ll the r ult of nattent on Regard ng tl e prınc ple of the rostral-cau lal pattern of sensory n rı t n or tle order of sensory lom na ce I woul l l ke to llu trate tl s l y a sl le (fig 8 The l ta ol a ed here are fron ol servat ons recorded on norn al cl l lren ages 3 to 6 years Nu rou trials of s ultaneou t ulat o of various coml nat ons of two bod parts l e bee n l You will ote that the face an l gen tal regio s ha e tle l gl est order of n l ce of co rect re ponses or n other words sl ow a h gl order of dom n ce Somewl ere n the d ll of tl e scale the foot and tl e lan l s the l ast correctl perce ved All our lata n tle f ce gen al and hand region ha e been foun l to be stat t call s gı fi ant I w ll o l scuss otl er body parts s nce there is little grad ent between each of tl m

N w f we accept tle tl eory of ro tral-caudal d trıl ut on of sensory lon na ce tl e quest on arises wl s tl e gen tal region so l gh ın tl s ord r be ng aln o t o the sa e le el a th fa e Secon lly wl y ıs the foot lo n nant o er tl e l and? Tl e ge tal regio an l tle f ot are rta l au lal to the hand I asked Dr Hooker pre ıously wl etl er or not l e at ten ı ed to n e t gate the ge tal regio n the fetus He sa d l e d d not ha e an oppc rtun ty t l s I real ze tl at l presentat on was of a prel n nary nature l ut I l ope h n l *fur* u w th n ore d ta n the future Tl s may shed further l ght o tl e rostral-cau lal tl eory f sens ry o gan zat on Tl e l le I sl owed you tod y llu trates a order of do n nance ı l lre wl l not ro tral caud l n l t l ut on

DR D EXPORT HOOKER (Clos g I an ery glad tl at Dr B n l r was ıted t l u tl paper At tl ıs t ne t ı not cl ar why the fetal han l contrary to h s fin l gs s d ant o er tl e foot It ıs l ope l that before we are tl rougl with our stud es we w ll *know* wl e f fan l d n n nee s prese t tl ro gl out fetal l fe Tl e cases presented l ere are qu te ung

more distal Of course, these conclusions are still tentative because of the small number of tests made Nevertheless, the uniformity of the resulting rostral dominance constitutes a definite trend If this trend is significant it would seem that the earlier established, hence older, reflex arcs dominate those which have appeared more recently and are thus younger, leading to their extinction Furthermore, this sequence of diminishing functional dominance in a cervicocaudal direction is in full accord, phylogenetically as well as ontogentically, with the inherited structural basis for activity

DISCUSSION

Dr William F Windle [Bethesda, Maryland] Mr Chairman, I would like first to express my appreciation of the research which Dr Hooker and his group have done over the years and to congratulate them on the excellence and thoroughness of it I must confess that I have not been so persistent in my study of prenatal development as he has been Although I started my program some twenty five years ago, I did not follow the main path but turned aside at every interesting lane along the way, while he went on to the more definite goal

One thing I would like to say is that we do not really know what the fetus does *in utero* In some species, we have learned a little about what it is capable of doing when removed but I am not so sure today that it makes a lot of difference what you can elicit from a fetus removed from its normal intrauterine environment and deprived of its oxygen supply

Perhaps it is not really important what the fetus does *in utero* but it is important to the fetus to develop in a way that will provide for any contingency to provide against premature interruption of its comfortable rest In the development of these little beasts we do see evidence of their preparation for sudden shift from intrauterine to extrauterine existence

I think you can see in some of these pictures of Dr Hooker anticipation of a need that will become urgent at birth namely respiration A basic movement of the small fetuses enters into the gasp becomes at least a part of the gasping mechanism a little later on This is one of the most fundamental requirements assuring that the individual be prepared at as early a date as possible to exist outside the uterus

The fetus must also be prepared to receive food We see early development of the trigeminal mechanism which will play an important part in nursing Of course we don't know very much about the digestive apparatus of the human fetus but in the guinea pig fetus it begins to function *in utero* long before the end of gestation The fetus swallows the contents of the amniotic sac concentrates material swallowed defecates *in utero* reswallowing and reconcentrating several times before it is born We know that most of this mechanism is able to function well in advance of the time it is called upon to do so

These are but two examples of the anticipation as it were by the growing fetus of need to survive long before normal interruption of intrauterine life

With regard to the questions of sequence of development and individuation from total pattern', little need be said for no new evidence has been brought forth Of course cephal[illegible] [illegible] inal cord and growth proceeds in a [illegible] roceeds rostrad from the bulb ir re [illegible] can elicit a bulbar type of activity

from the fetus, removed from its normal environment

Dr Morris B Bender To me Dr Hooker's work is of course interesting and important, and I think that these findings are significant from our point of view

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activities of the fetus depends upon the acuteness of her sensitivity Cases are known of pregnant women who have been able to feel activity at thirteen or fourteen weeks much before most women feel it This may prove nothing but I am convinced that it is an indication that fetal activity does occur normally *in utero* at a very early age

The sequence of fetal activities is so uniform that it is possible to determine the age of a given fetus by the kind of activity it exhibits I am convinced that the sequence presented is normal and is based upon developing structure The sequence is preparatory to the activities of later fetal and postnatal life If one compares Dr Gesell s series of voluntary capacities of the growing child with the fetal sequence, the child reduplicates in large part the fetal reflex sequence

Dr Windle suggests that all these movements are preparatory for respiration I have not so interpreted these early activities because a definite respiratory sequence quite different from these movements does appear later

There is a steady progression of capacity for reflex activity from the early embryo to the late fetus The organism can perform only those activities which the level of development of the neuromuscular system permits

These pictures were taken under an electrically operated camera placed over a constant temperature bath of saline The fetus when delivered is immediately taken to the photographic laboratory and placed under the camera Stimulation and photography are then begun

We have nothing to say about any operative procedures but we have advance notice to prepare Depending on their age fetuses may respond for periods from five to fifteen minutes until they can be resuscitated Some of the latter older group are still alive in Pittsburgh

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reflect the general course of child development in terms of behavior traits characteristic of advancing maturity levels (4 7, 11 12 13)

The motion picture records of the progressive ages were subjected to comparative study and to frame by frame time space analysis *The method* of cinemanalysis provides an objective approach to the developmental morphology of behavior It permits us to envisage the action system of infant and child as an architectured structured reality which assumes lawful forms primarily determined by embryological processes These processes establish an unbroken continuity of the prenatal and postnatal periods of behavior ontogenesis

From the standpoint of the embryology of behavior we shall consider evidences of innate growth factors in several directions as follows

1 Developmental stability of the fetal infant
2 Consistency of growth gradients and sequences
3 Cyclic trends of the growth complex
4 Developmental correspondence and individuality of twins

THE DEVELOPMENTAL STABILITY OF THE FETAL INFANT

Manifest behavior begins with the fetal period and organizes with great rapidity As an insurance factor against the contingency of premature birth the capacity for breathing is laid down at about the fetal age of 28 weeks which is 12 weeks prior to normal need The viable fetus becomes an infant at birth He is called a fetal infant from the time of his premature birth to the fortieth post-conception week

His precocious entrance into the world affords an opportunity to trace the course of behavior development which is usually concealed within the uterus A total of 80 systematic observations supplemented by cinema were made on 29 subjects at post-conception ages of 28 32 and 36 weeks For convenience we regard these ages as marking the early stage, mid stage and late stage of fetal infancy (5 7) Our findings indicate that prematurity uncomplicated by damage or disease has no permanent dislocating effect upon the ontogenetic sequence of behavior development

The early stage fetal infant (post-conception age 28 ...

... caused the eyeball moves conjointly the lids flutter the frontal brow or only half of it corrugates the tongue protrudes lips purse ...
a crying expres...
meager He lies ... he assumes quiescent and floating tonic neck reflex attitudes Movements are poorly sustained Torpor constantly supervenes

CHAPTER IX

BEHAVIOR PATTERNS OF FETAL-INFANT AND CHILD

With Evidences of Innate Growth Factors

ARNOLD GESELL[1]

Organisms behave. Their behavior traits are as distinctive as their physical traits. The human infant comes by his behavior as he comes by his body, through the organizing processes of growth. As behavior grows it assumes lawful forms, characteristic of the species and of the individual. This paper undertakes to assemble evidences of innate growth factors which underly the patterning of infant behavior and which must therefore have a bearing on problems of inheritance. For the moment the term 'innate growth factors' does not need to be defined too rigidly. It denotes a) endogenous maturational factors—the sum of gene effects; b) constitutional factors which become so established that they consistently influence the ontogenetic course of development.

ONTOGENETIC SURVEY OF BEHAVIOR PATTERN

Our studies at Yale University and continuing studies at the Institute of Child Development at New Haven are chiefly concerned with the ontogenetic sequences and gradients of normal behavior. A large array of behavior patterns has been charted and codified for 34 maturity levels from birth to the tenth year. This survey is being extended to embrace the years from ten to sixteen. During the first year of life a cooperative research group made systematic records at lunar month intervals. The resultant data were based on standardized behavior tests, naturalistic and clinical observations, and periodic motion picture documentation. Relationships between maturation and learning were explored by the method of co-twin control. Clinical studies of the mental growth of defective and atypical infants contributed to the formulation of general principles of development.

All told, some 3,000 concrete behavior items and patterns were identified in a cooperative survey of normal children. The data were classified in terms of growth gradations for 42 different behavior areas. These gradients

[1] Gesell Institute of Child Development, New Haven, Connecticut.

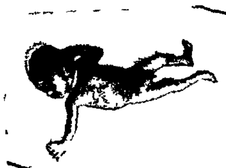


Fig 9 Right tonic neck reflex pattern in a fetal infant (age circa 32 post-conception weeks)

the other arm is flexed near the shoulder, the ipsilateral leg may share in the more or less tonic extension In configuration the pattern resembles a fencing attitude briefly or prolongedly sustained It is not a fixed stereo typed reflex but a growing complex which undergoes progressive maturity changes and is subject to individual variations It has a prenatal as well as postnatal psychology It is one of the most fundamental and pervasive behavior forms of the human action system It offsets the limitations of bilateral symmetry Elaborated and inflected it figures in adult acts of skill aggression and extrication (2 10)

The early postural habitus of the fetus is symmetrical Hooker (18) has noted that on facial stimulation the fetus of approximately 12 weeks reacts with a bilateral arm movement which approximates the hands toward the mid line This may be considered a precursor of symmetro tonic patterns (s t r for short) which appear in infancy It has also been noted that at a fetal age of about 20 weeks rotating of the head to one side tends to induce extension of the arm on that side This foreshadows a well defined t n r attitude which is manifested by the fetal infant at the early post conception age of 28 weeks (fig 9) The t n r is a marked feature of the spontaneous behavior of the full term infant during the first 12 weeks of life It comes into increasing coordination with visual fixation in *preparation for* prehension (fig 10) At 16 weeks unilaterality of posturing begins to wane the head rotates more freely and prefers the mid position, *simultaneously*, hands come to the mid line in bilateral *prehensory approach upon a dangling object* or to engage in mutual *fingering This* is a symmetro tonic pattern (fig 11) which in turn gives way to increasingly versatile unilateral and alternating patterns followed later by symmetric patterns at a higher level of manipulation The 28 weeks old grasps a single cube, exploits it by hand and mouth transfers and retransfers it from one hand to the other

At mid stage, *four weeks later, the fetal infant is less fragile*, more compact. His muscle tonus is less fluctuant and increases on manipulation. His head station is firmer and functionally more closely related to the trunk. He holds the tonic neck reflex attitude more tonically and at times windmills his extensor arm. On tactile cue he flexes on a rod with active grasp. His eyes open wider and more often. They do not fixate, but they respond saccadically in momentary pursuit of a moving object. Despite prevailing drowsiness, the mid stage fetal infant evidences a growing distinction between sleep and wakeness. There are brief periods of wakeful awareness and alertness.

During the late stage (from 36 to 40 weeks of post conception age) the sleep wakeness activity cycles become more clearly defined. Postural activity increases. Crying becomes more vigorous. The periods of visual and auditory awareness lengthen. The infant now falls off to sleep more decisively and clings to sleep more tenaciously. He wakes spontaneously (thanks to the primitive waking center of Kleitmann). He is physiologically *more robust, his muscle tonus is now well consolidated. Having had some* weeks in which to refine his adaptations to an extrauterine environment, the late stage fetal infant may function more smoothly than a full term newborn infant of comparable post conception age. But this apparent advantage is transient and does not confer any permanent acceleration upon the precociously born fetal infant.

The course of his behavior ontogenesis is well ballasted by intrinsic maturational determiners, and it tends to run parallel to the equivalent developmental sequences of the full term infant. *If*, for example, the fetal infant was born 8 weeks prematurely, we expect him to function at a 16 weeks maturity level when he reaches a chronological age of *24 weeks*, his true age being reckoned as 24 minus 8 weeks. This expectation is confirmed by cinema and by our clinical studies of uncomplicated cases.

The stability of early ontogeny has far reaching implications for the problems of psychological inheritance and of psychic constitution. Maturation is the intrinsic stabilizing component of development which determines the basic patterns of species and individual traits. It represents the net sum of gene effects (1, 6, 20, 21).

THE CONSISTENCY OF GROWTH GRADIENTS AND SEQUENCES

The role of maturation is further evidenced in the consistency of growth gradients and sequences. It is well illustrated by the developmental history of tonic neck reflex behavior. The tonic neck reflex (t n r for short) is an asymmetric pattern, best observed in the supine infant: the head is spontaneously turned to one side, one arm extends laterally to the same side

havior eye hand coordination, vocalization, percept concept formation, and postural behavior (12)

THE CYCLIC TRENDS OF THE GROWTH COMPLEX

In spite of a wide range of individual variations, the presence of innate ontogenetic factors becomes apparent, not only in the over-all movement toward specific ends but in the minor and major fluctuations of the growth cycle These more or less rhythmic fluctuations are manifest in the sequence of behavior patterns which leads to the assumption of upright posture and bipedal walking Twenty one developmental stages of *prone behavior (and quadrupedal progression)* are pictured in figure 12 (8) The double column arrangement emphasizes the developmental importance *of bringing flexor and extensor movements into reciprocal relationship*

The *shifts in flexor* and extensor predominance and in unilateral and bilateral phases are primarily growth phenomena They cannot be regarded as the product of cultural or environmental forces They are in the nature of sub-cycles within a total over all cycle of *ontogenesis (fig 13) Comparable sub-cycles* in numerous fields of behavior have been *identified throughout* the period of infancy and childhood Behavior *traits do not* form on an even front They are subject to innate *cyclical trends and to the accumulating* constitutional conditions which growth itself creates

From the standpoint of growth and *form* the organism is *under the* constant necessity of *reconciling opposed functions such as flexion* and extension and of bringing them into reciprocal relationships This is accomplished not by uniform *expansion* but by *an intricate* growth process of neuro motor interweaving (fig 14)

The [illegible]

lin [illegible]

pois [illegible] *results in the ascendancy of one function over to the other with progressive integration and modulation of the resultant behavior patterns* (3 8 12)

Neurologically (and behaviorally) this implies an intricate process of reciprocal interlacing and a *progressive* spiral kind of reincorporation at successive levels of maturity *Reciprocalness does* not necessarily mean symmetry Indeed there is a corollary *mechanism* of functional asymmetry which provides for unilateral *dominances and biased* sensory motor sets notably hand dness The *t n r pattern* is a striking example *of how* the organism achieves *such* unilateral orientations which lead to increased efficiency and localization *Interestingly* enough infants exhibit innate individual differences with respect to t n r [illegible]

differences [illegible]



Fig 10 Right tonic neck reflex pattern in a full term infant (age 6 weeks)

The 40 weeks old infant grasps a cube in each hand and brings them together combiningly at mid line in horizontal bilateral symmetry — another star pattern at a higher level of maturity (6)

At one year of age his manipulation patterns are again more unilateral. Using his preferred hand he superimposes one cube upon another by vertical approach. At 18 months he builds a (vertical) tower of three cubes; at two years, a (horizontal) wall; at three years, a bridge which combines horizontal and vertical spacing. Similar trends in directionality are displayed in the infant's spontaneous and imitative crayon strokes. The strokes move from serial to vertical to horizontal, circular and oblique. Comparable sequences have been demonstrated in varied fields of visual be-



Fig 11 Symmetro-tonic pattern in a full term infant (age 16-20 weeks)

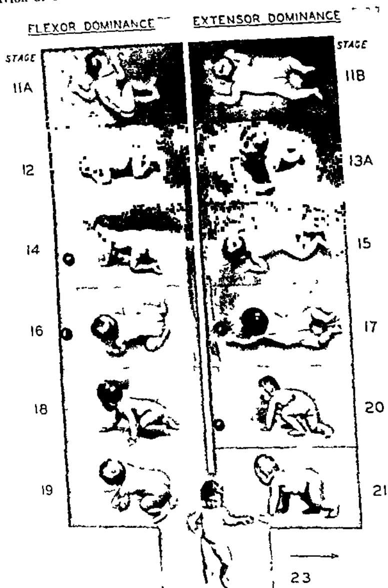


Fig 12—Continued

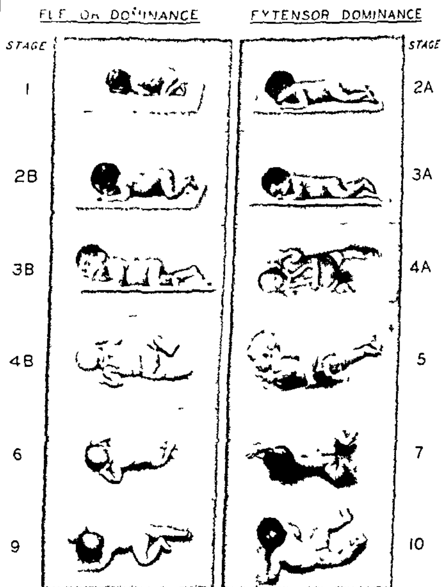


Fig 12 Twenty one stages of prone behavior, seriated to show growth trends of flexor and extensor dominance from 4 to 60 weeks

Each day a pendant lure was moved twice across her field of vision. Cinema records from the 15th to the 82nd day show 65 separate t n r postures only one of which was leftward. Despite the distraction of the lure a right t n r was maintained (14).

It should be noted that unidexterity or handedness is not a neatly packaged unit character trait which emerges sharply once and for all. It undergoes progressive organization through an alternation of phases of unilaterality and bilaterality whereby one hand becomes in varying ways accessory and subordinate to the dominant hand. These alternating phases were identified by analysis of annual cinema records of a series of seven single born children over a period of ten years. The graph of figure 15 illustrates the combined influence of reciprocal interweaving and functional asymmetry (9).

The weight of evidence indicates that handedness depends upon innate developmental factors but to what extent it is specifically determined by

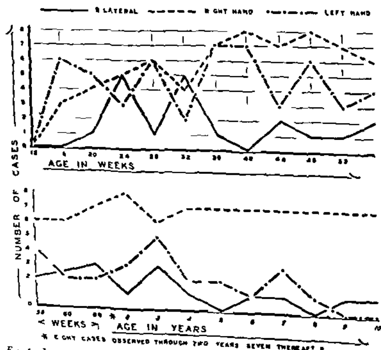


Fig 15 ... of period ... based on analysis

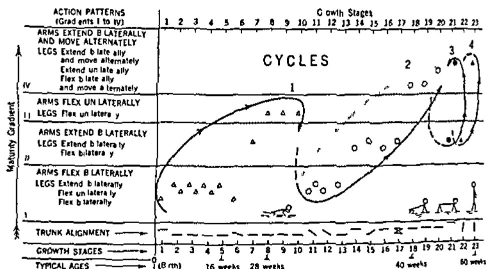


Fig 13 Cycles of growth in the patterning of prone behavior

heads in free head rotation. The great majority of fetal infants and full term infants showed an unmistakable preference for right as opposed to leftward orientation. Objective cinema analysis data were available for a group of 19 infants to determine their handedness at 1, 5, and 10 years. In 14 out of the total 19 cases the direction of the early t.n.r. was definitely predictive. In 5 cases it was ambiguous or contradictive. There were 4 cases in which left handedness was correctly foretold by a predominant left t.n.r. in early infancy (2, 10).

Another infant, M. H., who belonged to the right wing, was photographed daily in the supine position under strictly controlled conditions

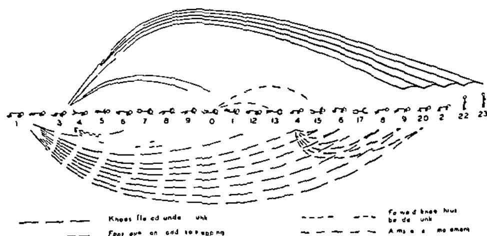


Fig 14 Reciprocal interweaving in the development of prone and upright locomotion

Each day a pendant lure was moved twice across her field of vision. Cinema records from the 15th to the 82nd day show 65 separate t n r postures only one of which was leftward. Despite the distraction of the lure a right t n r was maintained (14)

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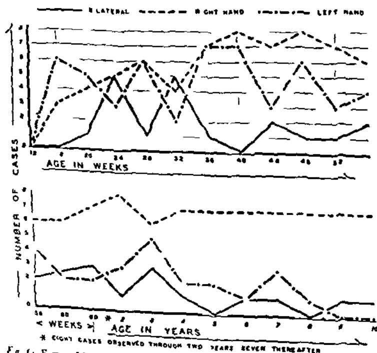


Fig 15 Forms of handedness most evident during the first ten years. Based on analysis of periodic cinema records of the natural behavior of seven to eight children



Fig 16 Developmental behavior examination of twins T and C Simultaneous horizon and zenith photographs show detailed similarity of postural and prehensory behavior patterns in response to a 7 mm pellet test Mirror imaging of crown hair whorls is diagrammatically indicated Twin T clockwise Twin C counter clockwise

genes is not clear, although left handedness is said to behave in inheritance as a Mendelian recessive It is difficult to explain why it should be almost twice as frequent in fraternal twins as in the general population The very high incidence of left handedness in monozygotic twins is more understandable Precisely equal cleavage of a zygote tends to produce mirror imaging which might conceivably bring about left handedness in a co twin Comparing a series of monozygotic twins on a zygote basis Newman found that asymmetry reversal (left handedness) appears four times more often in identical twins than in fraternal twins (19 22)

DEVELOPMENTAL CORRESPONDENCE AND INDIVIDUALITY IN TWINS

In 1927 the writer and co workers at the Yale Clinic of Child Development began a series of studies of the development of a highly identical pair of twins T and C shown in figure 16 (15 16, 17 21) The studies were equally concerned with developmental correspondences and disparities innate and induced We used the method of co twin control to analyze relationships between maturation and learning The course of development is still under observation and has been summarized in detail for the 14 years from early infancy to adolescence (16) [2]

The correspondences in physical and psychological traits have proved remarkable Behavior characteristics were periodically examined by systematic tests and recorded by cinema Repeated inspection and analysis of the film records have served not only to establish thoroughgoing similarities but also to define the distinctive individualities of the twins

Although the individual differences are slight they are consistent and

[2] The writer reported the early findings to the Association for Research in Nervous and Mental Disease in December 1933 (Proceedings volume XIV)

pervasive when the entire developmental record is critically reviewed The nature of these differences is indicated in a tabular summary of the patterns of attention contrastively *formulated* as follows

Attentional characteristics (H)

Twin T	Twin C
Prompt initial pick up	More deliberate initial pick up
Intense fixation	More relaxed fixation
Sharp focalization	More diffuse focalization
Decisive	Roving
Discrete	Confluent
Delimited	More sensitive to context and margins
Selective for details	More comprehensive and extensive
More varied adaptive exploitation	More imaginative exploitation
Specifically alert	More generally alert
Less intuitive in social situations	More intuitive in social situations

The foregoing differences are small in magnitude but they were detectable by means of co twin comparison and they suggest the operation of innate genetic factors Over the long stretch of 14 years the twins had not been separated except for very brief intervals No psychogenetic event in their personal or inter personal history or experiences could account for the durable differences which were first noted in infancy

The extensive motion pictures of the early development of the twins give objective evidence that many of the behavior differences were definitely foreshadowed in the first year of life Similar studies of single born children demonstrate the latent predictiveness of infant behavior traits

The growing child reveals his individuality not only [illegible]

[illegible] maturation being the sum total of gene effects Each infant exhibits a distinctive mode or pattern [illegible]

[illegible] in terms of an innate developmental morphology

[illegible]

[illegible] is concerned —the inheritance of integrated neuro psychiatric patterns With full recognition of the reciprocal interdependence of heredity and environment this paper [illegible] inherent factors [illegible]

patterning Env [illegible]

do not generate the progressions of development The organism uniquely contains the innate architectonic arrangements which can account for the developmental stability of the fetal infant, the consistency of growth gradients and sequences, the cyclic trends of growth, the developmental correspondence of twins, and the genesis of individuality

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CHAPTER X

THE TRIGEMINAL NERVE IN RELATION TO EARLY HUMAN FETAL ACTIVITY

TRYPHENA HUMPHREY[1]

INTRODUCTION

As pointed out by Hooker during this symposium (30) the human embryo first responds to exteroceptive stimulation at 7½ weeks of menstrual age (20 mm 18 20 7 mm 29) following stimulation of the nose mouth area. The resulting reflex consists of contralateral axial flexion limited to the cervical region. This reaction obviously involves the maxillary (and/or mandibular) fibers of the trigeminal nerve (29) and the ventral horn motor neurons in the cervical region of the spinal cord. In a recent paper (Humphrey 33 fig 4) in which the caudal extent of the spinal tract (or descending root) of the fifth nerve (V) was reported for human embryos, it was suggested that the descending fibers in this tract constitute the earliest pathway for transmission of the stimuli to the upper cervical region of the spinal cord. Connection with the contralateral ventral horn motor neurons is established by axons from the dorsal horn area which traverse the ventral white commissure to synapse with the motor neurons contralateral to the [illegible]

[illegible] ventral white commissure. Indeed, in human embryos only slightly over 5 weeks of menstrual age (7 mm in length), Windle and Fitzgerald (79 p 495) found that the axons of motor neurons extend well into the mesenchyme and some of these cell bodies [illegible]

[illegible] region (79) and by the seventh week it is especially well represented at the rostral end of the spinal cord (Windle

The physiological [illegible] which this paper is publi[illegible] Amer[illegible]

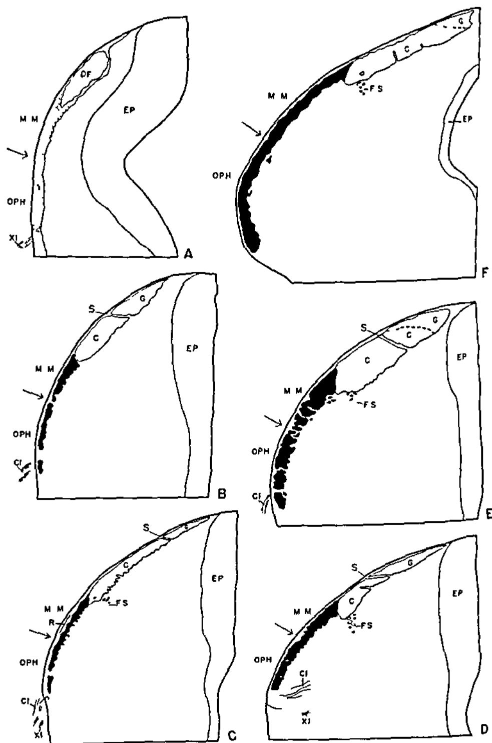


Fig 17 A series of drawings (magnification, × 75) of transverse sections of the spinal cord each taken at approximately the middle of the first cervical segment The spinal tract of the trigeminal nerve is either represented in solid black or the fibers shown by dots (A) The

and Fitzgerald 79 p 498) However at 5 weeks (6 mm human embryo, Wilson Windle and Fitzgerald, 75, p 294) the descending trigeminal fibers have been traced only a little beyond the entering vestibular rootlets From this age until about 8 weeks no observations on the spinal tract of V have been reported as yet Just under 8 weeks (22 mm), when the contralateral axial flexion response is readily elicited the maxillo mandibular division of the spinal tract of V has already grown through the first two cervical segments of the spinal cord and entered the third cervical segment (33)

Since the 1952 publication on the spinal tract of the trigeminal this fiber bundle has been studied in four additional specimens, two of which are younger in age (Homo 113, 14 mm, $6\frac{1}{2}$ weeks[3], Homo 93 V 20 7 mm, $7\frac{1}{2}$ weeks) one is in the 8 weeks age group (Homo 131 22 6 mm, just under 8 weeks) and one is older (Homo 134 34 3 mm, $9\frac{1}{2}$ weeks) Of these, the first two were prepared by the colloidal silver method of Bodian (5) and the last two by pyridine silver techniques All four were serially sectioned in the transverse plane at 10 μ The methods used to determine the caudal limits of the spinal tract of V and to differentiate the ophthalmic from the maxillo mandibular division of V are the same as those previously utilized (33) Summaries of the observations made on these four specimens, together with certain aspects of the findings reported in 1952 for the other fetuses will be presented in the following paragraphs

A small area relatively free of fibers (fig 17), present between the ophthalmic and the maxillo mandibular divisions of the spinal tract of V in fishes (see Kappers Huber and Crosby, 39, p 384 and fig 148, Crosby and Yoss 11) is also a constant feature in the human spinal tract of V through the age periods studied It is this fiber free zone (32, 33) which has been used to determine the border between the ophthalmic and maxillo mandibular portions of the spinal tract of V in the human fetal material The deeper staining reaction of the ophthalmic fibers in fishes, as compared

[3] The ages given for the material on which these and previously reported observations are made refer to menstrual age as determined in relation with the studies on fetal activity by Hooker (29 and earlier)

arrow pointing to the surface of the section shows the location of a small superficial area of the spinal tract of V relatively more free of fibers which ma ...
max llo ...
a
A
g ... 0 0 93 V 1,
... Homo 131 D 22 0 mm embryo just under 8 weeks
Homo 12 F 26 5 mm fetus $8\frac{1}{2}$ weeks Homo 19 F 34.3 mm fetus $9\frac{1}{2}$ weeks ...
C fasciculus cuneatus C1 dorsal ...
FP ependyma FS ...
d ... on of the s ...
fiber bundle fro ...
... tus S ...
... spinal accessory rootlets



Fig 18 Photomicrographs of sections through the first and second cervical segments of the spinal cord to show the spinal tract of the trigeminal nerve × 100 A 14 mm fetus 6½ weeks, Homo 113 Section rostral to the middle of the first cervical segment Activated protargol preparation according to the method of Bodian B 20 7 mm fetus 7½ weeks Homo 93A Section through the middle of the first cervical segment Activated protargol preparation according to the method of Bodian C 22 6 mm embryo just under 8 weeks Homo 131 Pyridine silver preparation A B and C are photographs of sections in the region used for the drawings in figures 17A, 17B, and 17C D is a section through the more caudal part of the first cervical segment of the spinal cord of the 22 6 mm fetus The arrows indicate the border between the dorsal funiculus and the maxillo mandibular fibers of the spinal tract of V

with the maxillo mandibular fibers is sometimes noted in the human material as well, but this difference is not of such constant occurrence. Thus it is the ontogenetic repetition of the phylogenetic trigeminal neural patterns (11) which has made it possible to distinguish the maxillo mandibular from the ophthalmic division of the spinal tract of the trigeminal nerve.

SUMMARY OF OBSERVATIONS ON THE SPINAL TRACT OF THE TRIGEMINAL NERVE

As early as $6\frac{1}{2}$ weeks (14 mm., figs. 17A and 18A), that is a week before the embryo responds to trigeminal stimulation, fibers of the spinal tract of the trigeminal can be identified in the spinal cord. These root fibers of V can be followed some distance into C1, although differentiation is not distinct enough in this colloidal silver preparation[4] (method of Bodian, 5) to determine either their final point of termination or make certain which fibers are represented farthest caudad.

At $6\frac{1}{2}$ weeks only a few fibers are present in the spinal tract of V but these are scattered through the characteristic site of this tract in the marginal zone ventral to the dorsal funiculus. Some of these fibers are isolated and others in small clumps of two or three so that their appearance is suggestive of the pioneering fibers of Harrison (26), Speidel (55, 56, 57, 59), Weiss (67, 68, 70, 71) and others. However, in spite of the limited number of trigeminal fibers found at this age, they are more numerous in two regions—near the dorsal funiculus (the location of the maxillo mandibular fibers) and near the accessory nerve rootlets (the position of the ophthalmic division)—with a more fiber free area between, as previously described at somewhat older ages (33). The majority of the maxillo mandibular fibers lie near the underlying gray matter or intermingled with its cells (fig. 18A) as noted by Crosby and Yoss (11) for the spinal tract of V in lower vertebrates.

At the age when contralateral flexion first follows perioral stimulation (at $7\frac{1}{2}$ weeks, 18, 29), the fibers of the spinal tract of V have increased greatly in number and already extend throughout the first cervical segment of the spinal cord. Their exact [illegible]

[4] Because colloidal silver preparatio[illegible] tracts the observations on the materi[illegible] Homo 33A) are less clear-cut. Indeed in fetuses over 8 weeks of menstrual age it has not been possible to identify the spinal tract of V in the spinal cord with certainty in the colloidal silver material.

C fasciculus cuneatus; C1 sensory rootlets of first cervical nerve; DF dorsal funiculus; FS fasciculus solitarius; G fasciculus gracilis; MM maxillo-mandibular division of spinal tract of V; OPH ophthalmic division of spinal tract of V; R sensory root fibers of the first cervical nerve which pass between the spinal tract of V [illegible]



Fig 18 Photomicrographs of sections through the first and second cervical segments of the spinal cord to show the spinal tract of the trigeminal nerve × 100 A 14 mm fetus 6½ weeks, Homo 113 Section rostral to the middle of the first cervical segment Activated protargol preparation according to the method of Bodian B 20 7 mm fetus 7½ weeks, Homo 93A Section through the middle of the first cervical segment Activated protargol preparation according to the method of Bodian C 22 6 mm embryo just under 8 weeks Homo 131 Pyridine silver preparation A B and C are photographs of sections in the region used for the drawings in figures 17A 17B, and 17C D is a section through the more caudal part of the first cervical segment of the spinal cord of the 22 6 mm fetus The arrows indicate the border between the dorsal funiculus and the maxillo mandibular fibers of the spinal tract of V

18D 20 and 22) Both maxillo mandibular and ophthalmic divisions decrease greatly in size in the middle third of C2 at this age as they do also at this level at all later stages studied In this portion of C2, where the spinal tract of V decreases markedly in size, large numbers of fibers from all of its divisions have been seen to turn into the dorsal horn for termination (25 mm embryo see Humphrey, 33 fig 12)

Examination of comparable levels of the first cervical segment between the ages of $6\frac{1}{2}$ and $8\frac{1}{2}$ weeks inclusive demonstrates that although the total area occupied by the spinal tract of V is increased during this period the dorsoventral extent of the tract is not greatly changed (fig 17 A to F) Comparison of the total spinal cord size, as seen in transverse sections through C1 at $6\frac{1}{2}$ 8 and $8\frac{1}{2}$ weeks shows that the major growth in the alar plate area during this time is mediolaterally (as cells proliferate into the mantle layer from the ependyma) and not dorsoventrally (fig 19) The slight increase in dorsoventral diameter of the alar plate during this time evidently depends upon the dorsal funiculus for this fiber bundle has about doubled in its dorsomedial to ventrolateral extent between $6\frac{1}{2}$ and $7\frac{1}{2}$ weeks the age at which fibers of fasciculus gracilis probably reach these spinal cord levels

The spinal tract of V may vary as to caudal limits of both ophthalmic and maxillo mandibular divisions in fetuses of essentially the same age In two such fetuses (22 mm and 22 6 mm see figs 20 and 22) just under 8 weeks although the spinal tract passes about an equal distance into the spinal cord in each case (fig 20) the termination with relation to the s [illegible]

[illegible] ophthalmic divisions may differ in fetuses of the same age (compare C and D of fig 17)

At $8\frac{1}{2}$ weeks when rump rotation and brachial extension [illegible]

[illegible] caudalward and the maxillo mandibular fibers may now pass through C3 or even into C4 (figs 21 22 and 23) although the great bulk of them in both divisions terminates in the middle third of C2 as at 8 weeks The fiber free area between maxillo mandibular V and ophthalmic V is still clearly visible in this fetus (fig 17E)

Although it was assumed (Humphrey 33 [illegible]

[illegible] report On the contr[illegible]

[illegible] age levels It now appears more

in this embryo (also a colloidal silver preparation in which there is little differentiation between individual fiber tracts), although the maxillo mandibular fibers can be identified caudal to those of the ophthalmic division Many more fibers are present in the spinal tract of V at this age (figs 17B and 18B) than at 6½ weeks, but they are still loosely arranged in little

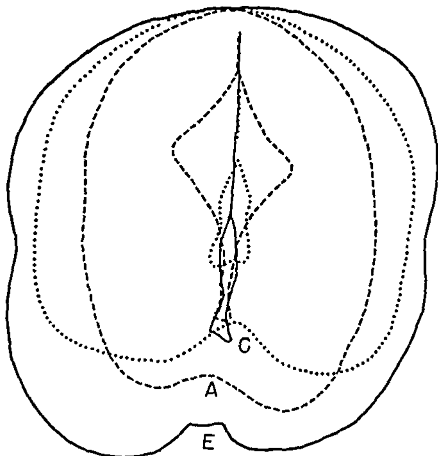
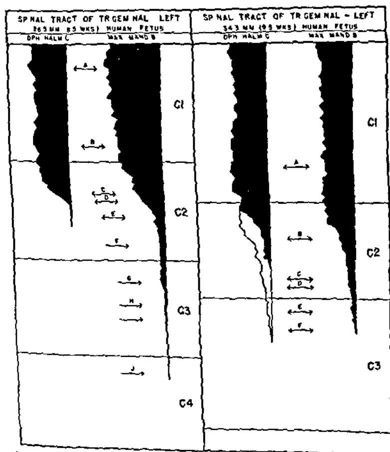


Fig 19 Outlines of the sections through spinal cord that are illustrated in figure 17 embryo C shown in dotted lines 22 6 mm ... be readily noted that the major increase in diameter of the first cervical segment during this period is mediolaterally with much less change in dorsoventral diameter

fascicles The fiber free zone between the maxillo mandibular and ophthalmic divisions of the tract is more sharply defined than at 6½ weeks

By eight weeks of menstrual age when contralateral axial flexion in response to perioral stimulation is well established the maxillo mandibular fibers of V have clearly outdistanced those of the ophthalmic division in caudal growth (22 mm, Homo 12 22 6 mm Homo 131) and can be followed throughout C2 (Homo 131) or even into C3 (Homo 12) whereas the ophthalmic fibers do not pass beyond the middle third of C2 (figs 18C,

of this age pass as far caudalward as do those of the other divisions (figs 21 22 and 24) This increased caudal growth of the ophthalmic fibers was also suggested earlier (Humphrey, 33 p 175) On the left side however the ophthalmic fibers still end cephalic to those of the maxillo mandibular



F g 21 Graphic representations of the sp nal tract of the trigeminal nerve in the cervical regi n of the sp nal cor l of t o human fetuses of 8 5 (Homo 19 26 5 n n) a d 9 ... 34 3 mm

... l the arrows l beled A to J are show n figure 23 ... ... zu ... t m l tus lrawn at the level sp nal cord of the 34 3 n n fet s lrawn at the le el of each of the arrows labeled A ... are shown n figure 24 The area ... p nal tract of ... m C2 and C3 ... of the left side (sol l black) ... ... n on the right side

probable, however, that the spinal tract of V has attained its most caudal termination point in the spinal cord by the time that the first local responses to trigeminal stimulation appear (30), i.e., by 9½ to 10 weeks of age. Inasmuch as the termination point in any two embryos of the same age may vary considerably (see fig. 20), it is probable that a comparable variation is present in the adult as indicated by Jimenez Gonzales (37). If so the spinal tract of V may sometimes pass further into C4 in the adult than has yet been shown by these studies of fetal material. It is equally possible that in some cases all of the tract may end in C3.

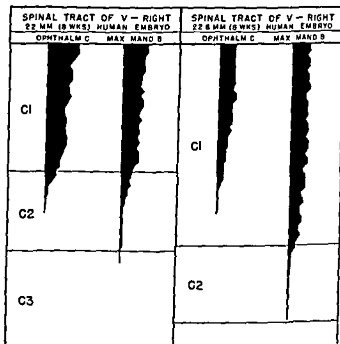


Fig. 20. A graphic representation of the size and extent of the spinal tract of the trigeminal nerve in the cervical region of the spinal cord of two human embryos of just under 8 weeks of menstrual age (Homo 12, 22 mm; Homo 131, 22.6 mm). The tract on the right side of the spinal cord is illustrated for each embryo. The limits of the spinal cord segments were determined on the basis of the distribution of the dorsal root fibers to the spinal ganglia. The graph was made by measuring the cross sectional area occupied by the maxillo-mandibular and ophthalmic divisions of the tract with a squared micrometer scale in the ocular of the microscope and plotting this measurement transversely on graph paper. By plotting the number of 10 μ sections vertically on the graph paper the actual limits of the spinal cord segments are proportionally represented (see Humphrey, 33, for further details). Note the variation in length of the different spinal cord segments and the differences in termination point of the subdivisions of the spinal tract of V with reference to the cord segments.

In spite of the fact that at 9½ weeks, the caudal limits for the spinal tract of V as a whole have not increased beyond the termination point for the tract at 8½ weeks, the ophthalmic fibers on the right side of the fetus

nant of the facial nerve also supplies fibers to the posteromedial aspect of the auricle

It has been suggested by Raney et al (48) that the central branches of the cutaneous fibers of VII, IX and X lie along the ventral aspect of the spinal tract of V in numerical sequence, with the fibers of VII most dorsally situated and those of X most ventrally placed From his observations following tractotomy, however, McKenzie (43) suggests that the fibers from the ear (and throat) lie adjacent to the mandibular fibers in the dorsomedial part of the spinal tract of V It is in this area that Wallenberg (63) believed the bucco lingual fibers of V to be situated and Winkler (80) located nasal and buccal fibers.

Although varying somewhat in position, even among the fascicles of the same cranial nerve, the rootlets of VII IX and X usually pass through the spinal tract of V in the region between and bordering on both the maxillo mandibular and ophthalmic divisions (Riley 49, pp 66, 72 and 80) In order to occupy the position indicated by Raney et al it would be necessary, then for the cutaneous sensory fibers of VII, IX and X to shift ventralward appreciably after entering the brainstem Consequently *it seems more likely that the somatic afferent fibers of these three nerves join the spinal tract of V near the area of their passage through this tract, as they do in some lower vertebrates (11) and alter their position only enough to bring them more or less between the maxillo mandibular and the ophthalmic fibers of V (region to which arrow points in fig 23 A and fig 24 A)* Such a location would also place the cutaneous sensory fibers of VII IX and X in the same relative position in the body pattern formed by the fibers of the dorsal funiculus and the spinal tract of V as they occupy peripherally This relationship is not surprising inasmuch as these fibers supply part of the ear a region which is innervated also by the mandibular division of V

MODE OF TERMINATION OF THE SPINAL TRACT OF V

During development sensory root fibers tend to be deflected into those nuclear centers that happen at the time to be undergoing cellular proliferation (Sperry 60 p 237 see also Coghill 9 10 Burr 7 Weiss 67) This tendency would account for the descending course of the cutaneous sensory root fibers in the spinal tract of the trigeminal nerve because the upper cervical cord region (the area of earliest neural tube closure) is undergoing rapid differentiation during the period when these fibers penetrate the rhombencephalon and turn caudad

Upon reaching the appropriate areas of termination in the brainstem and cervical spinal cord the descending trigeminal fibers establish synaptic relations with the secondary sensory neurons in the nucleus of the spinal

division. In this older fetus, at least, the fiber-free zone between maxillo-mandibular and ophthalmic divisions is small and often difficult to distinguish (fig. 17F).

POSITION OF THE CUTANEOUS SENSORY FIBERS OF VII, IX, AND X IN THE SPINAL TRACT OF V

In many lower vertebrates the facial, glossopharyngeal and vagus nerves, as well as the trigeminal, supply cutaneous sensory fibers for the face (11, 39). In man, the vagus supplies the concha of the ear and the posterior wall of the external auditory canal (12) and a twig of the glossopharyngeal

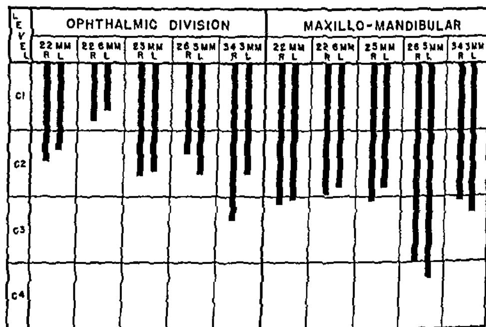


Fig. 22 A graphic representation of the ophthalmic and maxillo mandibular divisions of V for both right and left sides of the spinal cord of 5 human fetuses from 22 mm to 34.3 mm in crown rump length (just under 8 weeks to 9.5 weeks of menstrual age). For this figure the cross sectional area occupied by the tract has been disregarded and only its rostrocaudal extent illustrated. All of the spinal cord segments are represented of equal length and the terminal point *for each tract estimated on the basis of the percentage of the* segment traversed by the division of the tract in question. In this way the proportionate distance that each division has penetrated into the segment in which it terminates is readily compared throughout the group of fetuses. Note the variation between the ophthalmic division on the right (R.) and that on the left (L.) for each fetus.

nerve may distribute with it (41). Likewise Larsell and Fenton (42) found that a branch of the facial nerve joins the auricular branch of X and concluded that it probably supplies the auditory meatus, the tympanic membrane and part of the concha. According to Hunt (34), this vestigial rem-

nant of the facial nerve also supplies fibers to the posteromedial aspect of the auricle

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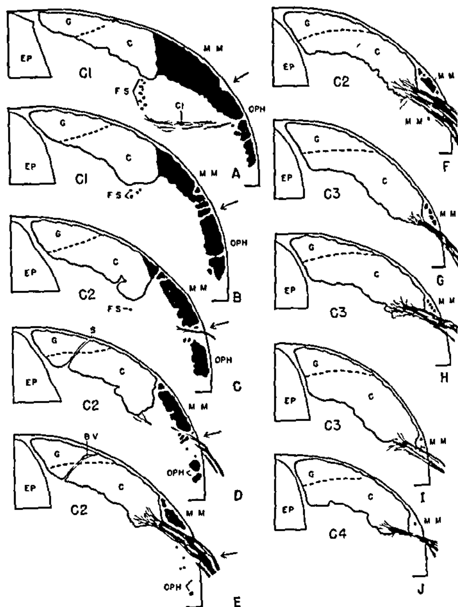


Fig 23 A series of drawings from the left dorsal horn area of the spinal cord of the 8½ weeks fetus illustrated in figure 21, made at a magnification of 75 Each of the drawings labeled A through J was made at the level of the arrow similarly labeled in figure 21 The arrows pointing to the surface of the spinal cord in 23A through 23I mark the border between the maxillo mandibular division of V dorsally and the ophthalmic division ventrally The broken line crossing the dorsal funiculus marks the approximate border between fasciculus gracilis and fasciculus cuneatus

B V blood vessel in dorsal intermediate septum area, C fasciculus cuneatus, C1 first cervical segment of spinal cord and sensory rootlets of first cervical nerve, C2 C3, C4 second third and fourth cervical segments of the spinal cord, EP ependyma FS fasciculus solitarius, G fasciculus gracilis, M M maxillo mandibular division of spinal tract of V, OPH ophthalmic division of spinal tract of V, S dorsal intermediate septum

tract of V. Undoubtedly the pain fibers of the spinal tract of V branch as they terminate in its nucleus, so that those carrying pain from adjacent cutaneous areas overlap each other at their termination centrally as well as peripherally (19). Certainly such a central overlap is present for the pain carrying fibers of spinal nerves (20).

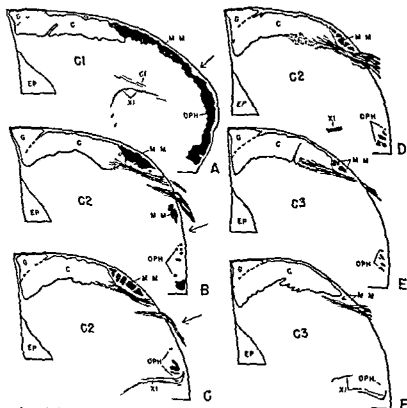


Fig. 24. A series of drawings from the left dorsal horn area of the spinal cord of the 9½ weeks fetus illustrated in figure 21, made at a magnification of 75. Each of the drawings labeled A through F was made at the level of th

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accessory nerve

The ventral secondary ascending tract of V transmits impulses aroused by painful stimuli from the nucleus of the spinal tract of V to nucleus ventralis posterior of the thalamus (from which they are relayed to the sensory cortex). In order to lose all perception of pain carried by the trigeminal nerve after section of its spinal tract in the medulla (trigeminal tractotomy of Sjoqvist 52) it is evident that this tract must be severed above the most cephalic point of distribution of its fibers to the secondary pathways. Tests for pain perception following trigeminal tractotomy performed just cephalic to the motor decussation have frequently revealed such a complete loss of pain perception from all areas supplied by the trigeminal nerve (21, 22, 43, 66). If some pain perception over V is retained McKenzie has found it most often in the region of the upper lip. It may be concluded, then, that all secondary ascending fibers related to pain perception over V arise just cephalic to the motor decussation, at the level of this decussation and caudal to it in the gray matter of the upper cervical spinal cord segments in which the spinal tract of V terminates. Were this not true there could be no complete loss of perception of trigeminal pain following section of the spinal tract of V just cephalic to the pyramidal decussation as has been observed by Groff and Levy (22), Grant and Weinberger (21), Weinberger and Grant (66), McKenzie (43) and others.

The loss of pain perception over all areas supplied by mandibular V after trigeminal tractotomy performed at the upper border of the motor decussation (see Grant et al. 21, 66, Groff et al., 22 and McKenzie 43) demonstrates clinically that the mandibular division, as well as the other divisions of V, passes below the rostral limits of this decussation. Observations on the human fetus show that, morphologically, the most significant decrease in the number of fibers in any division of the tract takes place in the middle third of C2. Consequently, failure to relieve pain along the mandibular division of V by trigeminal tractotomy at midolivary levels (i.e., well above the motor decussation), or even higher, is not due to termination of these fibers above the level of section, as apparently believed by some neurosurgeons (17, 23, 45), but rather to failure to direct the cutting instrument so that the mandibular fibers are included in the operation.

Since the observations on human fetuses demonstrate that all divisions of the trigeminal nerve pass into the spinal cord, these results favor the interpretation of Woods (81), Dejerine (13), Brouwer (6) and others on the manner of termination of the pain fibers in the spinal tract of V. However, these pain fibers must come into synaptic relation with the cells of origin of the ventral secondary ascending fiber system only at caudal levels of the medulla and in the spinal cord (just above the motor decussation

at motor decussation levels[4] and in the cervical cord portion of the nucleus of the spinal tract of V (see fig 25) and not throughout the medulla oblongata as implied by Dejerine (13) Nevertheless within this more limited region of distribution of the pain fibers the results of pain perception tests following trigeminal tractotomies support a distribution according to the onion skin pattern of Dejerine with fibers from trigeminal zones which are adjacent to the cervical nerve distribution ending in the most caudal part of the nucleus of the spinal tract of V Thus it has been noted (38) that trigeminal tractotomy at caudal levels may allow perception of painful sensations in zones about the nose and mouth although sensitivity to pain is lost in those regions of trigeminal distribution which lie next to C2 Similarly as noted previously, following trigeminal tractotomy performed at a level which does not eliminate pain perception completely (McKenzie 43 5 mm below the obex) any residual retention of pain perception is most often located about the upper lip Continued careful observations on

Although tactile sensation is not lost following trigeminal tractotomies which result in loss of pain perception over the distribution of all three divisions of the trigeminal nerve Weinberger and Grant (65 66) found an increase in the threshold for tactile stimulation and a decrease in the number of tactile spots after tractotomy in comparison with those present on the unoperated side even when the operation was performed at more caudal levels Such observations indicate that there is some overlap at least between the levels of termination of pain fibers and the distribution of general tactile fibers to those neurons of the nucleus of the spinal tract of V which contribute to its ventral secondary ascending tract (see fig 23) Adequate tactual tests following section of the spinal tract of V at caudal levels have not been reported The presence of medullated fibers of the spinal tract of V in upper C2 as shown by myelin sheath stains (54 C2 80) suggests that tactile fibers may reach this level However some pain fibers of the trigeminal nerve such as those innerv

(31)

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[4] According to Carlton Smith (53) the motor decussation is overlapped by the level of origin of the ventral roots of the first cervical nerve

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Reflexes resulting from trigeminal stimulation, such as swallowing tongue movements and the corneal reflex, are not lost in the adult when the spinal tract of V has been sectioned just above the motor decussation (McKenzie, 43, and others) Since these reflexes (referred to as local reflexes in fetal behavior studies, see Hooker, 29, and Humphrey, 33) are retained at least part of the connections mediating them must be established above the level of section of the spinal tract of V, i e, above the motor decussation

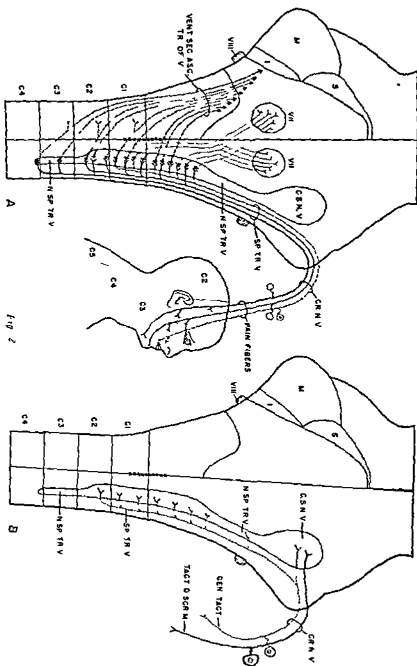
Although many of these trigeminal reflexes in the adult are normally related largely, if not exclusively, to the general tactile fibers of V, the corneal reflex has customarily been associated with the pain fibers alone, and only free sensory endings[6] have been identified in the cornea (82) It

[6] Following trigeminal tractotomies which result in loss of corneal sensitivity to pain corneal stimulation may give rise to a sensation described as touch (17, 51 52) According to Zander and Weddell (82) a dilute solution of Pantocaine in the conjunctival sac will prevent the perception of the customary sensation of pain upon corneal stimulation although a *sensation akin to touch is felt if the stimulating agent deforms the cornea These observers* suggest that this crude sensation of touch may be related to the terminations found in the tunica propria of the cornea whereas the painful sensations result from stimulation of the terminations in the corneal epithelium

Fig 25 A Diagram to illustrate the probable distribution of the cutaneous sensory fibers in the spinal tract of the trigeminal nerve and the levels of origin of those fibers of the ven*tral secondary ascending tract of the trigeminal which transmit pain to the nucleus* ventralis posterior of the thalamus The outline drawing of the head is modified from Dejerine s figure 378 (13) to show 3 zones of the face rather than 5 The pyramidal decussation (small cross es in the midline) is illustrated as overlapping the first cervical cord segment (53) In conformity with observations on human embryos that maxillo mandibular fibers of V may reach C4 fibers of the spinal tract of V are shown at this level In accordance with observations of neurosurgeons made after trigeminal tractotomy the fibers from the nose mouth region are illustrated as terminating highest in the nucleus of the spinal tract of V and those from areas bordering the cervical nerve distribution as terminating farthest caudalward in the spinal cord The pain carrying fibers of the ventral secondary ascending tract of the trigeminal are shown as taking origin only from spinal cord and lower medulla levels—at the level of the *motor decussation just above it and in the first four cervical levels of the spinal cord*

B Diagram to show the termination of the tactile fibers in the spinal tract of the trigeminal nerve Two types of tactile fibers are illustrated as demonstrated by Windle (76) non bifurcating fibers for tactile discrimination which terminate solely in the chief sensory nucleus of V and bifurcating general tactile fibers which end in both the chief sensory nucleus and the nucleus of the spinal tract of V In agreement with observations reported following trigeminal tractotomy the general tactile fibers are shown to terminate in the upper cervical *cord levels and to overlap the region of distribution of the pain fibers*

C S N V chief sensory nucleus of the trigeminal nerve CR N V root fibers of trigeminal nerve GEN TACT general tactile fibers of trigeminal I inferior cerebellar peduncle M middle cerebellar peduncle N SP TR V nucleus of the spinal tract of V S superior cerebellar peduncle *SP TR V spinal tract of the trigeminal* TACT DISCRIM tactile discrimination, VENT SEC ASC TR OF V ventral secondary ascending tract of the trigeminal, VII facial nucleus VIII eighth cranial nerve


VENT SEC ASC TR OF V
VIII
M
I
S
VII
VII
C S N V
N SP TR V
N SP TR V
SP TR V
CR N V
PAIN FIBERS
C1
C2
C3
C4
C5
A
Fig 2
VIII
M
I
S
C1
C2
C3
C4
N SP TR V
SP TR V
N SP TR V
C S N V
GEN TACT
TACT O SCR M
CR N V
B

Reflexes resulting from trigeminal stimulation, such as swallowing, tongue movements and the corneal reflex, are not lost in the adult when the spinal tract of V has been sectioned just above the motor decussation (McKenzie, 43, and others). Since these reflexes (referred to as local reflexes in fetal behavior studies, see Hooker, 29, and Humphrey, 33) are retained, at least part of the connections mediating them must be established above the level of section of the spinal tract of V, i.e., above the motor decussation.

Although many of these trigeminal reflexes in the adult are normally related largely, if not exclusively, to the general tactile fibers of V, the corneal reflex has customarily been associated with the pain fibers alone, and only free sensory endings[6] have been identified in the cornea (82). It

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Fig. 25. A, *Diagram to illustrate the probable distribution of the cutaneous sensory fibers* in the spinal tract of the trigeminal nerve and the levels of origin of those fibers of the ventral secondary ascending tract of the trigeminal which transmit pain to the nucleus ventralis posterior of the thalamus. The outline drawing of the head is modified from Dejerine's figure 378 (13) to show 3 zones of the face rather than 5. The pyramidal decussation (small crosses in the midline) is illustrated as overlapping the first cervical cord segment (53). In conformity with observations on human embryos that maxillo mandibular fibers of V may reach C4, fibers of the spinal tract of V are shown at this level. In accordance with observations of neurosurgeons made after trigeminal tractotomy, the fibers from the nose mouth region are illustrated as terminating highest in the nucleus of the spinal tract of V and those from areas bordering the cervical nerve distribution as terminating farthest caudalward in the spinal cord. The pain carrying fibers of the ventral secondary ascending tract of the trigeminal are shown as taking origin only from spinal cord and lower medulla levels—at the level of the motor decussation, just above it, and in the first four cervical levels of the spinal cord.

B. Diagram to show the termination of the tactile fibers in the spinal tract of the trigeminal nerve. Two types of tactile fibers are illustrated as demonstrated by Windle (76): non bifurcating fibers for tactile discrimination which terminate solely in the chief sensory nucleus of V and bifurcating general tactile fibers which end in both the chief sensory nucleus and the nucleus of the spinal tract of V. In agreement with observations reported following trigeminal tractotomy, the general tactile fibers are shown to terminate in the upper cervical cord levels and to overlap the region of distribution of the pain fibers.

C.S.N.V., chief sensory nucleus of the trigeminal nerve; C.R.N.V., root fibers of trigeminal nerve; GEN. TACT., general tactile fibers of trigeminal; I, inferior cerebellar peduncle; M, middle cerebellar peduncle; N.SP.TR.V., nucleus of the spinal tract of V; S, superior cerebellar peduncle; SP.TR.V., spinal tract of the trigeminal; TACT. DISCRIM., tactile discrimination; VENT.SEC.ASC.TR.OF V, ventral secondary ascending tract of the trigeminal; VII, facial nucleus; VIII, eighth cranial nerve.

reflex is followed shortly by other reflexes (deglutition, orbicularis oculi contraction, etc.) in the sequence given by Hooker.

The possibility that the selective elimination or addition of collateral branches may be one of the ways in which local responses become established during the development of behavior was mentioned by Sperry (60, p. 276). The sequence which Hooker (30) reports for the appearance of local trigeminal reflexes raises the question as to whether the *order of development* of collateral branches from the stem fibers in the spinal tract of V may not be a major factor in determining the sequence of development of local trigeminal reflexes. With this possibility in mind the data available on the time of development of collateral branches, together with the various factors which determine the appearance of collaterals along an axon, will now be considered.

Information is very meager as to the time of appearance of collaterals in the course of development of fiber tracts. For the spinal tract of the trigeminal nerve in cat embryos Windle (78, p. 656) reported that the first collaterals are not found until after the descending fibers have at least passed the level of the vestibular division of VIII. The branches which then appear (in 10 mm. embryos), however, are at the level of entrance of the fifth nerve. It seems likely that these branches are the ascending limbs of the general tactile stem fibers as they pass to the neurons which will form the chief sensory nucleus of V (76) and therefore are not really collaterals at all. A little later Windle (78, 11.5 mm. cat embryos, p. 656) noted a few true collaterals from descending fibers of V at the level of the vestibular division of VIII (the location also of the caudal part of the facial nucleus). For the dorsal funiculus Windle and Fitzgerald (79, p. 497) found that a continuous white column was established in human embryos before any collateral branches are given off. Likewise Windle (77, p. 79, cat) found no branching of fibers in the ventral commissure until after the commissure is well developed.

The

and els

point anches are permanently established. As described by Weiss (68, p. 164), "A nerve process elongates by amoeboid activity at its tip. This free end is in a constant state of unrest, sending out pseudopodia in various directions, of which one usually establishes itself while the others are hauled in." During the growth of the fiber, this process is repeated over and over until the point of axonal termination is reached (Weiss, 68, p. 165). According to Weiss (68, 70), the preferential route for this fiber growth is in the direct line of the axis of the fiber. Thus although each pseudopodium represents a potential branch, Weiss (71, p. 454) points out that various forces tend to keep the axoplasm from flow

would appear, then, that at least a part of the reflex connections between the pain fibers from the cornea and the appropriate motor reflex centers of the brainstem must be established at levels cephalic to those contributing to the fibers carrying pain to nucleus ventralis posterior of the thalamus. Although it is possible that special fibers in the spinal tract of V are reserved for the mediation of reflexes, and do not make connections with the ventral secondary ascending fiber system, it seems more likely that reflexes resulting from stimulation of the sensory fibers of the trigeminal are dependent upon collateral branches from the stem fibers in the spinal tract of V which establish connections with the appropriate motor nuclei by way of internuncials. Inasmuch as the corneal reflex is retained following tractotomy which eliminates pain perception over the entire peripheral distribution of V, collaterals related to the production of this reflex (in response to stimuli normally producing painful sensations) must come off, in part at least, cephalic to the termination of the pain fibers of V for synapse with the ventral secondary ascending fibers related to pain perception (fig. 25).

THE ORIGIN OF LOCAL REFLEXES IN RESPONSE TO TRIGEMINAL NERVE STIMULATION

Up to 9½ weeks of menstrual age the only response to unilateral trigeminal stimulation is contralateral (rarely homolateral) axial flexion (at 7½ weeks) which becomes more extensive as the fetus increases in age and is then accompanied by brachial extension and rump rotation (29). It has already been pointed out that during this age interval there is an increase in the number of fibers in the spinal tract of V and an additional growth of its fibers caudalward through two or even more spinal cord segments. As the contralateral flexion response extends to include rump rotation and brachial action, fiber systems other than those first functioning may take part in the response or even dominate it. It is possible that neurons in the sensory nucleus of V distribute impulses to reticulo-spinal fiber systems (2) which extend, reinforce or largely take over the contralateral flexion response. It is also probable that such spinal cord integrating mechanisms as the propriospinal systems likewise participate. In any event until 9½ weeks no functional connections have been made between any part of the sensory nucleus of V and the efferent neuronal systems which later produce localized reflex responses to stimulation of the trigeminal nerve.

The earliest local response to trigeminal stimulation reported by Hooker (30) is incomplete but active mouth opening first seen at 9½ weeks. The mouth closure which follows active mouth opening at this time is due to relaxation of the active muscles (see p. 148) and not to contraction of muscles which close the lips or elevate the mandible. This mouth opening

eral nerve fibers should also regulate the development of collaterals from fibers in central nervous system fiber tracts

Side branching also occurs where the growing fiber tip meets other fibers of any type crossing its path (27, 55 67 69, 70) That levels where the spinal tract of V is crossed by other cranial nerve fibers (VII VIII IX and X) provide a comparable stimulus for collateral formation is indicated both embryonically and phylogenetically Thus Windle (78) *found* the first true collaterals from the spinal tract of V at the level of the vestibular fibers of VIII (where fibers of VII cross the spinal tract of V, see p 145) and Crosby and Yoss (11) report the first development of collaterals in *lower vertebrates* at the levels at which cranial nerves enter the brain stem

Of the various factors known to influence the formation of collateral branches mitotic activity near an axon and crossing nerve fibers appear to be of particular significance to the order in which collaterals may be given off from stem fibers in the *spinal tract of V* Since differentiation of the brainstem occurs in a cervicorostral (30) direction from the point of closure of the neural tube in the cervical *region* (caudocephalic Kingsbury 40 p 309) the gradient of cellular proliferation in the brainstem as a whole follows this order as well More specifically it is evident *from our* own material that the nucleus of the spinal tract of V *differentiates* in a cervicorostral direction embryonically *just as* it does in the *course of* phylogeny (11) As the appearance of collateral branches is influenced by the presence of mitotic activity *sprouting of* side branches from stem fibers in the spinal tract of V should also tend to appear in a somewhat cervicorostral sequence *Other factors* influencing the format[illegible]

later [illegible]

axo[illegible]

earl[illegible] *es at these levels particularly* as has also been found to occur phylogenetically (11) Still other factors such as maturation of one center stimulating the development of functionally related nuclei may also *participate* With the data in mind as to the mode of development of collaterals *from stem fibers the sequence for the appear*ance of reflexes related to the spinal tract of the trigeminal will now be considered

If the spinal tract of V establishes *its* connections in a cervicorostral sequence then local reflexes mediated *[illegible]* more caudally *situated* motor [illegible] he first local reflex noted for [illegible] well as for the *rat* (1) and [illegible] (9) is active but in the human fetus incomplete *mouth* opening (30) Although in *normal* adult man active *mouth* opening is produced in large part by muscles innervated by V *through* midpons levels and by VII *through* more caudal *regions* of the pons certain suprahyoid

ing into more than one channel Consequently, as soon as a mass of protoplasm passes into one pseudopodium the others are automatically drained and withdrawn (see also Weiss, 68, p 175)

Such observations suggest that collateral branches from stem fibers in a tract probably do not usually establish connections before the axons have attained some degree of maturity, although some collaterals evidently begin development and are lost (55, 58) Indeed Edds (16, pp 266 7) specifically states that collaterals of regenerating peripheral motor axons do not appear until the fibers have matured to a certain point In discussing modes of fiber branching Weiss (67, p 536) is even more explicit for he says that "lateral excrescences—so called collaterals—bud out from the *stem* of an established nerve fiber", i e, presumably one which has made terminal connections (see also Weiss, 70, p 15)

Because axonal growth is by means of protoplasmic flow along the main axis of a fiber (25, 26, 68, 70) added growth in length of the neuraxis will tend to cease when its terminal synaptic relations are established As long as protoplasm formation in the perikaryon (35, 36 70 72 74) and flow along an axon continue at a rate greater than required to maintain it the formation of collateral branches will be favored Evidently this period of growth and differentiation of the neuron is an inherent property for each neuron type (Weiss 70, p 18) and is a significant factor in determining the number of collateral branches produced the size of the perikaryon and other characteristic features of the different classes of neurons

The appearance of collateral branches seems to be dependent upon a variety of other factors as well Among them are mechanical or chemical irritation (55 67 68 69) Obstructions in the path of a fiber may also influence its branching (55 59 67) According to Speidel (55 56 58) mitotic activity of neurilemma cells of fibroblasts or of myoblasts near a peripheral axon supply an excitant factor for collateral branch formation Under these conditions collateral branches are put out toward the dividing cells In the central nervous system no doubt mitoses of neuroblasts and glioblasts function in a comparable capacity i e provide an excitant factor for collateral branching A peripherally denervated zone (cutaneous or muscular) may also induce new side sprouts from adjacent intact peripheral nerve fibers (14 15 16 24 28 56 58 64 73) In the development of the central nervous system groups of neuroblasts which have not established synapses should provide a similar stimulus for the formation of collateral branches According to Sperry (61 p 72) the available evidence warrants the conclusion that synaptic linkages are regulated on the same principles throughout the nervous system If in the development of synaptic linkages the same principles apply both to peripheral nerves and to the central nervous system then the factors which determine collateral branching from periph

Deglutition brought about also by motor neurons of the medulla (nucleus ambiguus and nucleus hypoglossus), has been observed as early as 10½ weeks for the human fetus (30) However, in most studies of infrahuman fetal behavior swallowing has not been noted at all It may be that both tongue movements and swallowing depend more particularly on stimulation of the inside of the mouth in early fetal life at least and an adequate stimulus for these reflexes has only rarely been provided during the studies of fetal behavior

Most of the other local reflexes in response to trigeminal stimulation (30) depend upon the facial nucleus for their execution Of these, the contraction of the orbicularis oculi muscle appears first (at 10½ weeks) but is soon followed by action of the corrugator supercilii (at 11 weeks) Lip closure, which probably involves the motor nucleus of V (elevation of the mandible) as well as the facial nucleus does not occur until 12½ weeks

The contraction of the orbicularis oculi muscle on stimulating the skin of the eyelid is obviously the fetal counterpart of the corneal reflex in the adult Evidently this reflex is mediated largely, if not exclusively, through the caudal part of the spinal tract of V and its nucleus for various neurosurgeons (Olivecrona 45 and others) have found it to be lost entirely when the spinal tract of V has been sectioned above the caudal end of the fourth ventricle i e rostral to the obex region That a part at least of the reflex pathway is related to caudal levels of the medulla if not to the upper spinal cord is indicated by the fact that the corneal reflex is slowed or diminished when the spinal tract of V is sectioned at caudal levels of the medulla (Falconer 17 McKenzie 48 Kahn et al, 38 and others) If the corneal reflex is mediated ...

... rostral sequence of development of reflex collaterals from the spinal tract of V

As the preceding discussion indicates, local reflexes in response to trigeminal stimulation have been demonstrated by human fetal behavior studies to appear in a sequence suggestive of a cervicorostral pattern of development of the central nervous system mechanisms involved Consequently it is suggested that the order of appearance of the ...

and infrahyoid muscles innervated by the first three cervical nerves[7] do participate and can partially open the mouth when the other muscles are not able to act (44, 50). In fetal life, then, if reflex arcs through upper cervical levels for innervation of these supra- and infrahyoid muscles were completed earliest in development, an incomplete but active mouth opening should be the first local reflex to appear. This is exactly what happens for the human fetus as well as for rat and guinea pig fetuses. Active jaw closure, however, since it is mediated entirely through the motor trigeminal nucleus at midpons levels, would appear later in fetal life than mouth opening, as it has been found to do, not only for the human fetus (Hooker, 30, lip closure at $12\frac{1}{2}$ weeks, 3 weeks later than mouth opening) but also for the rat (Angulo, 1, 3 days later) and the guinea pig (Carmichael, 8, one day later).

According to Angulo (1) tongue movements appear as early in the development of the behavior pattern of the rat as does mouth opening. In other studies of mammalian fetal activity these movements have not been observed until somewhat later in development and not until 14 weeks for the human fetus (Hooker, 30). In the course of phylogeny, the hypoglossal nucleus, which innervates the tongue muscles, becomes a discrete entity by the rostral migration of neurons from the motor columns of the ventral horn of the spinal cord (39). According to Barnard (3) the frog is the lowest vertebrate to show a hypoglossal nucleus separate from the ventral horn neurons, although in the frog the caudal part of the hypoglossal nucleus overlaps the ventral horn cells. In adult mammals, due to additional rostral migration of the hypoglossal nucleus, its rostral end has reached about the same cephalic level as the rostral tip of the dorsal nucleus of the vagus (39). In human fetuses at the time mouth opening appears the hypoglossal nucleus is still in continuity with the somatic efferent neurons of the first cervical segment of the spinal cord (46). If collaterals from the spinal tract of V form connections with the internuncials in its nucleus in a cervicorostral direction, the caudal position of the hypoglossal neurons would favor an early appearance of reflex tongue movements as Angulo found for the rat. Probably such movements do occur in younger human fetuses than they have been noted heretofore but have not been observed because *the mouth is usually closed at this time* (30).

[7] The anterior belly of the digastric and the external pterygoid muscle are innervated by the trigeminal nerve and the posterior belly of the digastric and the platysma are innervated by the facial are the most significant muscles in active mouth opening in the normal adult. However, the infrahyoid (sternohyoid, Moyers 44, pp. 28)) and suprahyoid muscles do participate and can partially open the mouth when the other muscles are not able to act (44, *50*). The suprahyoid muscles which participate are the geniohyoid which depresses the mandible and the sternohyoid, the omohyoid and the thyrohyoid which cause lowering of the hyoid bone and so indirectly tend to lower the mandible as well.

sequence in which collaterals develop and establish functional relations with effector nuclei through interneurons in the nucleus of the spinal tract of V may be an important factor in determining the order of development of local reflexes in response to stimulation of cutaneous areas of the face. In connection with this suggestion the various factors which influence the formation of collateral branches of axons are discussed.

DISCUSSION

DR. ELIZABETH C. CROSBY [Ann Arbor, Michigan]: There seem to me to be three points of particular interest in Dr. Humphrey's account for the present discussion.

The first of these is that she has established an anatomical pattern which forms the basis

... of the lips as a region of stimulation for the early fetal movements.

Finally, she has indicated very clearly that the pattern established in normal fetal development reveals relations of significance for an understanding of the sensory losses exhibited by adult patients following trigeminal tractotomies.

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involve internuclear connections from the sensory nucleus of V to the effector nucleus (or nuclei) to complete the reflex arcs and the efferent neurons concerned may extend for some distance longitudinally in the brainstem, the order of appearance of collaterals from the fibers of the spinal tract of V will be only one of several factors determining the sequence of appearance of the local reflexes obtained upon stimulation of the sensory distribution of the trigeminal nerve

SUMMARY

The development of the spinal tract of the trigeminal nerve in human embryos is reviewed and data given from four additional specimens A few fibers of all three divisions of the spinal tract (or descending root) of V reach the spinal cord in embryos as young as 6½ weeks of menstrual age and the tract is present throughout the first cervical segment of the spinal cord by 7½ weeks when the first reflex can be elicited in response to perioral stimulation By 8½ weeks a few fibers of the maxillo mandibular portion of the spinal tract of V may pass into the fourth cervical segment of the spinal cord although in a fetus as much as a week older the spinal tract of V cannot be followed throughout C 3 These findings suggest that by 9½ to 10 weeks when the first local reflexes in response to trigeminal stimulation can be demonstrated, the spinal tract of V has attained its final termination point in the spinal cord Ophthalmic fibers which do not extend as far caudalward at 8 to 8½ weeks as do the maxillo mandibular fibers may be found equally far caudalward at 9½ weeks

It is concluded from observations in the literature on loss of pain perception following section of the spinal tract of V that all secondary trigeminal fibers transmitting pain to nucleus ventralis posterior of the thalamus take origin from caudal portions of the nucleus of the spinal tract of V—just cephalic to the motor decussation at the level of this decussation and caudal to it in the spinal cord levels in which the spinal tract of V terminates From the results of tests of tactual sensitivity following such operations it is concluded that there is some overlap in the nucleus of the spinal tract of V, between the origin of the fibers of the ventral secondary ascending tract of V which carry pain and those which mediate tactile sensitivity

The location of the cutaneous sensory fibers of VII IX and X with reference to the spinal tract of V is discussed It is suggested that these fibers occupy the area where the maxillo mandibular division of V borders on the ophthalmic division

The relation of the developmental sequence of local reflexes following trigeminal stimulation to the order of appearance of collateral branches from the fibers in the spinal tract of V is discussed It is suggested that the

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CHAPTER XI

THE HISTOGENESIS OF THE SPINAL CORD AND THE EARLY DEVELOPMENT OF BEHAVIOR

DONALD H. BARRON[1]

All those who have studied the subject appear to be in agreement that the early behavior of an individual of a given species of vertebrate develops in an orderly predictable fashion characteristic of that species and further that the expansion of the behavior pattern is a manifestation and a consequence of the regular and progressive differentiation of the function and configuration of the individual cells that together form the nervous system. These two generalizations lead quite naturally to the question: Do the early behavior patterns of all vertebrates develop in a similar fashion? In other words, does the early development of individual nerve cells and their pattern of organization into a system follow a similar course in all vertebrate embryos and fetuses? On this point, so important to the recognition of the principles that govern the ontogeny of the functional matrix of the nervous system, there is at present no general agreement, despite the fact that the development of the gross morphology of the central nervous system is recognized to have fundamental features characteristic of all vertebrates.

Instead of agreement there are currently two hypotheses or generalizations with regard to the pattern of the early development of behavior in vertebrates—each with a supporting body of data in the literature. The first, historically, was advanced by Coghill (10) on the basis of his detailed studies on the structural and functional development of the central nervous system of the larval salamander Amblystoma, i.e., behavior develops from the beginning through the progressive expansion of a perfectly integrated total pattern and the individuation within it of partial patterns which acquire various degrees of discreteness. No one has challenged the validity of this generalization in reference to the description of the development of the early behavior in Amblystoma, but its wider applicability to the genesis of functional maturation of the nervous system in other forms including mammals and man as Coghill suggested has been contested by W. F. Windle (23) and his collaborators, whereas Hooker (13) has interpreted his studies on man in support of it. On the basis of studies on the

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of the early behavioral patterns The interaction of nerve cells as conduc
... serve to modify the geometry of individual neurons and so be

Some evidence bearing upon these considerations is ... the literature it is reviewed here together with some additional data to draw attention to the importance of an understanding of the growth potentialities of neurons and the forces that guide them as antecedents of behavior but more specifically in relation to the problem does the motor system of the warmblooded vertebrates develop from a group of segmentally arranged units that are later organized into a whole by the longitudinal conducting systems or as a longitudinal unit that first responds totally and is only subsequently as development advances so modified by the influence of local afferents that the total response may be inhibited or fragmented and local reactions emerge by segregation Or put in other words does the pattern of the early differentiation of the motor system of the brachial cord in mammalia proceed in a manner compatible with Coghill s generalization with regard to the genesis of behavior or in accordance with Windle s view Unless they are qualified the remarks apply to the differentiation of the brachial motor system of the sheep embryo as observed in silver impregnated sections of a closely graded series of embryos of known ages

THE HISTOGENESIS OF THE MOTOR NEURON

Differentiating motor neuroblasts are present in the ventral portion of the lateral margin of the medullary epithelium (Innenplatte of His) of the basal plate of the brachial cord segments on the 21st day after insemination in the sheep they are situated in the outer third of the epithelial layer and distributed in the dorsoventral plane above medial to and below the level at which the axons of those most advanced in their differentiation converge at the external limiting membrane to form the ventral root (4) In silver preparations the stages of differentiation that can be recognized at this early age are in the order of their increasing development apolar bipolar and unipolar cells The apolar cells (neuroblasts of Held) are not easily identified in these silver preparations for the capacity for impregnation at this stage of their differentiation is less marked in those of the basal plate of the spinal cord than it is in other regions of the neural tube This delay in the development of the capacity for impregnation may be associated with the loci of their first appearance In the cere

development of the reaction patterns of avian embryos and mammalian fetuses, including man, Windle has advanced the view that behavior in these two classes of vertebrates has its genesis, not in a mass reaction or total pattern like that of lower vertebrates but in relatively simple reflexes which are at first entirely nonintegrated.

The acceptance of the second alternative—Windle's view—implies that there is a fundamental difference in the order and pattern in which the early development of the control of the trunk and limb musculature is established in mammals as contrasted with lower vertebrate forms, notably the Amphibia; such a difference in principle would appear to be surprising in view of the similarities in the more gross aspect of neural development, though it may be, as I have suggested elsewhere, that difference is one of *developmental sequence rather than principle, i.e., to be associated with* the earlier appearance of the limb relative to the differentiation of the spinal cord in the higher as compared with the lower tetrapods (8). In any event, the issue is unresolved and it would appear likely to remain so unless the problem can be approached from new angles, for the principal technique that has been employed in the past for the analysis of the early patterns of neural function in birds and mammals, including man, has been simple observation of the motor responses to tactile stimuli or to deformation. The nature of the responses and the circumstances under which they occur are such that two observers looking at the same reaction will frequently disagree in their interpretation of its nature, as to whether it is an isolated reflex, a total response, or the response of muscle to directly applied stimuli. Until some recording device can be developed that will *provide objective evidence of the nature of the responses,* further experiments along this line are not likely to be very fruitful, although when made on older fetuses whose responses can be interpreted in terms of the well recognized principles of synaptic and neuromotor transmission such observations yield valuable data on behavioral development.

As it is only the very early reactions of the embryo that are in question, the avenue to a broader understanding of the genesis of behavior would appear to lead through a study of the histogenesis of the conducting elements of the mammalian central nervous system—after the pattern of Coghill's analysis of Amblystoma—a study of the details of the manner *and sequence in which the individual neuroblasts acquire their varied* forms, i.e., the orientation of their processes in space and their organization into conducting systems. This accomplished, a basis would be provided for a comparison of the order and pattern of differentiation in different forms as the substrate for function and, finally, for the discovery of those forces that determine the patterns of function or behavioral development, for it is generally agreed that growth forces alone determine the character

tion of the neuroblasts in the more cranial segments, for none of the axons has as yet entered the primitive limb bud which is at a stage of differentiation similar to that in the three day chick, i e, a crescent of material opposite the brachial segments

As the motor neuroblasts accumulate on the outer margin of the medullary epithelium with increasing age, they first form and later contribute to the mantle layer of the basal plate As they arrive in the mantle, the apical dendrites of those that arise in the epithelium are withdrawn, the more advanced in their differentiation are accordingly all unipolar, the majority having reached that stage without passing through the bipolar Within the mantle the cell bodies of the neuroblasts shift their relationship to the direction of their axon and orient themselves in the dorsoventral plane As a result of this shift the long axes of the cells tend to parallel the lateral surface of the spinal cord an orientation they tend to keep as the addition of further cells from the epithelium to the mantle forces the position of the motor root ventralward from its original position on the lateral surface There are, of course neuroblasts in intermediate positions but with advancing development they join one or the other of the groups of neuroblasts that accumulate respectively above and medial to the ventral root exit except in the region of the cord that gives rise to the phrenic nucleus In that region some of the intermediately placed neuroblasts shift at a later time to a position in the mantle intermediate to the groups above and medial to the ventral root These two groups into which the motor neuroblasts are aggregated as early as the 24th day after insemination establish the medial and lateral subdivisions of the ventral horn though there is nothing to distinguish the cells in the one group from those in the other at this stage but their position and that appears to have been determined almost exclusively by their individual level of origin within the medullary epithelium

THE ORGANIZATION OF THE MOTOR CELL COLUMNS

In the adult sheep the columnar arrangement of the motor neurons of the brachial cord is a relatively simple one Named in the order of their position from ventromedial to dorsolateral they are [illegible] rsomedian, [illegible] teral The [illegible] remainder [illegible] attention [illegible] appear to be directly and indirectly associated with the appearance and development of dendrites on the neuroblasts that are resident in the lateral division of the ventral horn of the sheep embryo toward the close of the 24th day after insemination The cones of growth on some of the axons that extend from motor cells in the lateral division

more commonly in its outer margins The first bipolar stage of motor neuroblast differentiation is not constant as to site but appears to occur more frequently in those areas in which the medullary epithelium is thick and the cells tend to be arranged in a fairly regular columnar fashion These bipolar neuroblasts appear to spring from the more deeply situated apolar neuroblasts and to represent a stage in migration toward the lateral surface of the medullary epithelium, for those apolar neuroblasts that first appear in the lateral surface of the medullary epithelium do not appear to go through this stage of differentiation The two processes appear simultaneously, or nearly so, on the medial and lateral surfaces of the neuroblasts establishing its long axis, which is always at right angles to the long axis of the cord These two processes extend from the cell body in a direction more or less parallel to the radii formed by the columnar pattern of the epithelium This pattern may, in turn, be determined by the radial arrangement of the spongioblasts The process extended from the lateral surface of the neuroblasts is the more coarse It stains more heavily with silver and ends in a typical cone of growth The internal or centrally directed process the more delicate and lightly stained, ends in a fine point some distance from the internal limiting membrane At this first appearance however there is often so little difference in their character that the possibility must be entertained that the forces that determine the polarity of the neuroblast are external to it One has the impression that the spherical apolar cell is subjected to a greater pressure from above and below—dorsoventrally that is—than is applied to the mediolateral direction If this impression is correct the surface tension might be expected to be reduced on the medial and lateral surfaces from which the two processes are extended to establish a polarity The special features that distinguish the two processes—one as an axon and the other as a dendrite—may result from differences in the features of the environment into which they extend The centrally directed process is withdrawn as the cell body of the neuroblast shifts from the more dense and compact portion of the medullary epithelium to its more loosely organized lateral margin The axons of the motor neuroblasts whether they stem from the unipolar or less advanced bipolar cells are directed radially from the cell body at a right angle to the long axis of the cord none were discovered that grow tangentially along the cord The axon leaves the cord at the same level as that of the cell body They converge from above and below to an area on the lateral surface of the cord opposite the central region of the mass of differentiating neuroblasts where they pass directly through the fiber free marginal layer to gain the periphery and form the ventral root

The appearance of the spinal cord is at this stage of differentiation similar at all brachial levels aside from slight advances in the differentia

the ventral commissure The dendrites of some enter the commissure, cross to the opposite side of the cord and end either in the medial portion of the ventral funiculus or the ventromedial portion of the contralateral ventral horn The apical dendrites of others turn ventralward before reaching the commissure and enter the medial portion of the homolateral ventral funiculus Dendrites that arise from the apices of motor neuroblasts in the external half approximately, of the lateral portion of the ventral horn—that mass of cells dorsal to the ventral root—grow dorsalward Those arising from neuroblasts adjacent to the marginal layer follow its inner margin dorsalward some distance before they enter its substance The dendrites of cells more deeply placed in the mantle follow a similar, though somewhat less regular course but all appear to end near or in the marginal layer The number of neuroblasts that extend dendrites from the lateral half of the ventral horn appears to be fairly uniform at all brachial levels By contrast apical dendrites first appear on the neuroblasts situated in the more medial portion of the horn opposite the caudal end of the 6th cervical vertebra and from this area differentiation appears to spread cranially and caudally The apical dendrites as they grow dorsalward tend to converge above the area occupied by the cell bodies and terminate just short of the marginal layer

This difference in the courses taken by the dendrites of the medial and lateral halves of the aggregate of motor neuroblasts situated above the ventral root in the 25 day sheep cord serves to divide the motor cells of the lateral division of the ventral horn into two groups The more lateral division becomes the ventrolateral motor cell column of the adult cord, the more medial the dorsolateral All of these apical dendrites regardless of the site of their parent cell are perpendicular to the long axis of the cord and toward the funicular system

Between the 25th and 30th days of development the mantle area dorsal to the ventrolateral and dorsolateral cell columns is expanded by the addition of cells from the medullary epithelium that do not stain with silver Their small spherical bodies appear to be devoid of cytoplasm and processes I have called them indifferent cells for convenience and without any implication as to the nature of their latent potentialities As the apical dendrites of the neuroblasts of the dorsolateral groups grow dorsalward toward the marginal layer many of them enter the area newly occupied by the indifferent cells The arrival of these processes among the indifferent cells coincides with the first appearance of differentiating neuroblasts that have arisen in situ from these indifferent cells The axons from these newly formed neuroblasts grow ventral ... root and ...
cell

of the ventral horn into the premuscle masses of the dorsal longitudinal system and proximal portions of the limb are replaced, toward the 25th day of gestation in the sheep embryo, by primitive motor type endings. The character of these primitive endings varies widely in form but in general they resemble endings described in the smooth muscles of adults. The cone is replaced by two or three bead like expansions on the end filament or by beads in a series on a single filament (see fig 26). As development advances the axon itself branches, each major branch bears in turn the bead like expansions—the forerunners of the end plate. At the same time that the cones of growth are being replaced by primitive motor endings,

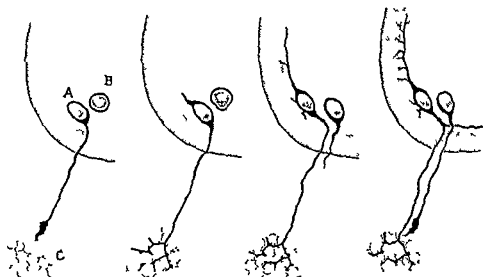


Fig 26 Diagrams illustrating the associated central and peripheral aspects of a motor neuroblast at successive stages in differentiation. A Motor neuroblasts. B An indifferent cell that first takes on the characteristic of a unipolar neuroblast when the neighboring cell extends its apical dendrite. C Myoblasts in the region of the termination of the axons.

motor neuroblasts resident in the cell groups, the one medial, the other dorsal to it, begin to put forth apical dendrites and become bipolar. These two events appear to take place at about the same time on an individual neuroblast, for Cajal (9) pointed out that permanent dendrites as these are first appear on a neuroblast at or about the time its axon arrives at its destination, an observation that has been repeatedly verified. (The suggestion has been put forward (Barron 7) together with some supporting evidence from experiments on the chick that these two events are causally related, i.e., that unless the axon tip reaches appropriate tissue in the peripheral field the dendrites do not appear on the cell body.)

As the apical dendrites appear on the most advanced neuroblasts in the medial division of the ventral horn of the sheep cord, they grow toward

ians and reptiles having in mind those features that might bear upon the nature of the early behavioral responses as interpreted in the contrasting views of Coghill and Windle outlined earlier? To what degree does the ontogeny of the conducting elements of the cord recapitulate their phylogeny?

First there is no evidence of any segmental grouping of the motor cells in the brachial segments either in their origin or in their arrangement in columns in the sheep cord the organization appears to be continuous rather than discontinuous and longitudinal This conclusion was not unexpected in view of the great body of evidence derived from experiments indicating that the segmentation of the spinal cord and peripheral nerves is molded by and secondary to mesodermic metamerism represented by the myotome and its derivatives and that an intrinsic nervous segmentation is nonexistent (11) Second as the axons leave the cord at the same level as that in which the cell body is located and further, since the axon does not give off any branches within the cord that run longitudinally in it there is no evidence to suggest that the motor neuroblasts of the mammalian and chick cord ever pass through a stage of differentiation in which they are both internuncial elements in a caudally conducting system and effectors as the earliest functional motor neurons are in the larval Amblystoma and other anamniotes

Third there is a marked similarity in the pattern of the early dendrites extended by the motor neurons of the chick and sheep in the developmental stages just described and that which is characteristic of the adult cord in fish amphibians and reptiles moreover there is a real similarity between the origin of the axon from the cell body and that observed in these forms There are according to Cajal (9) three principal stages in the evolution of the neuron in the first the cell body is smooth and bears but one process the axon which gives off at its origin smooth dendrites It is this type that is characteristic of the invertebrates as well as of Amphioxus and Myxine In the second evolutionary stage the cell body is provided with smooth dendrites and a robust extension of the body gives origin to the axon This stage is said to be characteristic of the medullary cells of the cords of the fishes amphibians and reptiles In the third stage the cell body is bristling with numbers of thorny dendrites and gives rise either directly or indirectly to the axon at the base of a protoplasmic expansion the axon hillock Cells of this type characterize the cords of adult birds and mammals If this classification is accepted as representing a phylogenetic sequence it is clear that the ontogenetic stage attained at the close of the description of their growth as outlined here corresponds closely to that of the second stage in phylogeny characteristic of the cold blooded vertebrates

There is another feature of the organization of the embryonic cord in

to appear and the one whose circumstances of origin differ from all of the others

Here again, there is evidence from experiments on chick embryos which indicates that the appearance of the dendrites on a neuroblast serves to initiate the differentiation of the adjacent 'indifferent' cells into neuroblasts (7, 16, 17)

As differentiation advances, secondary dendrites appear on the motor neuroblasts that form the columns whose origin has just been sketched The next in order, after the primary or apical dendrites, usually arise from some point on the axonal pole of the cell Strong, robust processes, they grow in a direction more or less parallel to the external surface of the mantle layer toward the ventral root exit, before they too turn outward into the funiculus The subsequent pattern of dendrite growth is less regular than the early, but with rare exceptions they tend to arise either from the poles of the neuroblasts or from the lateral surfaces of the polar dendrites and to be directed outward toward and into the funiculi Certainly one of the most striking features of the pattern of the dendrite growth at this stage is the almost complete absence of processes that extend into the central mass of cells that will eventually form the dorsomedial aspect of the ventral horn, another is the arrangement of the dendrites in a place more or less parallel to the long axis of the cell body and at right angles to the long axis of the cord (see fig 26)

The description of the development of the motor neuroblasts of the brachial cord of the sheep, sketched above and ending at the 34th day, the stage of first reactivity, would apply as well to the development of the individual motor neuroblasts that contribute their axons to the ventral roots of the brachial cord in the chick, provided one recognizes these differences (6), the differentiation proceeds more rapidly in the chick and in comparable stages of development—3rd to 6th day in the chick, 20th to 34th day in the sheep—there is no organization of cell columns within the lateral division of the ventral horn The dendrite pattern of the motor cells in the lateral division of the ventral horn of the chick cord is strikingly like that of the ventrolateral and dorsolateral cell columns of the sheep in their relationship to the funicular system and the surface of the gray matter as is that of the medial division of the ventral horn and the ventromedial cell column of the sheep Thus at the stage at which the brachial neuroblasts first activate their associated musculature, the basic pattern of their organization appears to be similar in the chick and the sheep

With these facts about the early development of the motor neuroblasts in the bird and the mammal in mind, attention may now be directed to the question: How does the early development and organization of the motor cells in these classes compare with that found in the fishes, amphib-

of

There is one further aspect of the organization of the mo[illegible] of the brachial cord of the sheep at the end of the premotile stage of development that deserves consideration—the composition of the cell columns, for they might be expected to represent a degree of segregation of the individual motor cells Indeed, there have been innumerable attempts to relate the cells within these columns with the motor supply to specific muscle groups and to associate the position of a motor cell in the ventral horn with the locus of the peripheral termination of its axon Despite the attractiveness of these schemes and their variety, none seems to have won general acceptance A part of the answer as to why they have not done so may be found in the studies of Sprague (20) on the peripheral distribution of the axons of the motor neurons of the sheep cord of 24 days

At that stage in development the number of neuroblasts heavily impregnated with silver is sufficiently small so that it is frequently possible, as Sprague has done to follow an axon from its cell body of origin into the ventral root and beyond until it enters one of the primary divisions—dorsal or ventral of the mixed spinal nerve—and so to test the view that the axons of the motor neurons lying ventromedial to the motor root exit supply the derivatives of the myotome—dorsal longitudinal musculature through the dorsal primary ramus whereas the cells in the columns of the lateral division of the ventral horn supply the derivatives of the lateral plate the limb musculature—via the ventral primary division of the spinal nerve Sprague's observations (see fig 28) make it clear that at this stage of development there is no selective distribution for axons from neurons in the cell columns of the lateral division of the ventral horn can be traced into the dorsal primary ramus of the segmental nerve and cells in the ventromedial column supply axons to the ventral primary ramus

These observations of Sprague's are in accord with the results of my own unpublished studies made in an effort to determine the central location of the motor cells supplying specific muscle groups and or segments in the fore limb of the sheep Selective destruction of muscle groups and the amputation of limb segments were carried out in utero on fetuses of known gestation ages The individuals were delivered at the end of term, some 70–80 days postoperatively the cords were prepared for, and studied in celloidin sections that were cut serially The Gudden's atrophy in these cases was pronounced With the opposite side of the cord as the control cell maps of the individual columns were made and the differences in these pattern on the two sides related to the characters of the peripheral lesion The studies indicate that with the exception of the retrodorsolateral, which has not made its appearance by the 24th day—the age at which

these early stages that is characteristic of the cold blooded vertebrate, i e, the relationship between the dendrites of the motor cells and the funicular fibers (fig 27) This arrangement appears to be a primitive characteristic for one of the most striking features of the ganglionated *chain of the invertebrates* is the existence of plexuses or molecular zones devoid of neurons in which contact is established between the axons of some cells and the dendrites of others A similar arrangement is to be seen in the lateral and ventral funiculi of the cold blooded vertebrates the

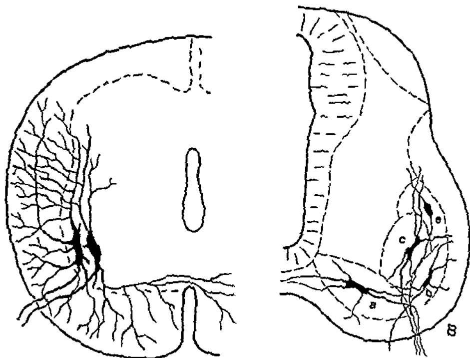


Fig 27 Diagrams illustrating A The orientation of the motor cells in the spinal cord of an adult amphibian and the relationship of their dendrites to the funicular system B the similarity in the orientation of the motor cells and their dendrites in the spinal cord of a thirty four day sheep fetus

axons of the funicular systems together with their collaterals mingle with the dendrites of the motor horn cells to form a plexus within the marginal layer This same pattern is repeated in the early developmental stages in the cord of the warm blooded forms with this difference the funicular fibers do not appear to give off collaterals that end or arborize in the marginal layer In the adult birds and mammals there is scarcely any trace of this earlier pattern of organization The dendrites are withdrawn from the funicular system and as will be pointed out later the collaterals of the funicular fibers invade the central gray as development advances Important for our purpose is the recognition of the similarity between the early

There is one further aspect of the organization of ... the brachial cord of the sheep at the end of the premotile stage of development that deserves consideration—the composition of the cell columns, for they might be expected to represent a degree of segregation of the individual motor cells Indeed there have been innumerable attempts to relate the cells within these columns with the motor supply to specific muscle groups and to associate the position of a motor cell in the ventral horn with *the locus of the* peripheral termination of its axon Despite the attractiveness of these schemes and their variety, none seems *to have* won ...

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These observations of Sprague's are in accord with the results of my own unpublished studies made in an effort to determine the central location of the motor cells supplying specific muscle groups and/or segments in the fore limb of the sheep Selective destruction of muscle groups and the amputation of limb segments were carried out *in utero* on fetuses of known gestation ages The individuals were delivered at the end of term, some 70–80 days postoperatively the cords were prepared for, and studied in celloidin sections that were cut serially The Gudden's atrophy in these cases was pronounced With the opposite side of the cord as the control, cell maps of the individual columns were made and the differences in their pattern on the two sides related to the characters of the peripheral lesion The studies indicate that with the exception of the retrodorsolateral, which has not made its appearance by the 24th day—the age at which

Sprague's studies were made—the population of all other columns was reduced by any lesion that involved the musculature proximal to the radio-humeral joint, though no column was obliterated. These observations suggest that the cells representing any muscle or group of muscles in the

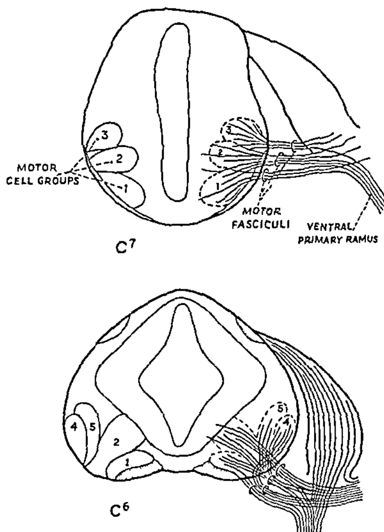


Fig 28 Diagrams illustrating the peripheral distribution of the axons arising in specific motor cell groups of the sheep cord of a twenty one day embryo at C 7, and at C 6 in an embryo twenty four days (after Sprague)

proximal segments or *trunk musculature* are widely distributed in the ventral horn. The apparent exception to this generalization is the retrodorsolateral column, its cells degenerate as a consequence of intrauterine amputation of *the limb at the radio-humeral joint, i e , the axons of its* cells are predominantly distributed to muscles that act over the wrist

joint This group of cells—the retrodorsolateral—appears then to be peculiar not only in its mode of origin as pointed out earlier, but in its organization for its axons tend to be distributed to a specific segment of limb musculature whereas the axons of the cells in the other columns are not so restricted in their distribution The latter represent a generalized rather than a selective or segmental pattern of organization

No similar study appears to have been made with regard to the functional localization of motor cells within the ventral horn of the chick but it is of interest in this connection that Cajal (9) figures axons from neuroblasts in the lateral division of the ventral horn of the five day chick cord entering the dorsal primary division of the spinal nerve to be distributed among myoblasts of myotomic origin If this figure is truly representative of the organization of the motor system of the chick at this stage, the implication is that in the chick as well as the sheep there is no precise functional organization of the motor system of a segmental character at this stage of development

ORGANIZATION OF CORD AT STAGE OF FIRST REACTIVITY

The organization of the motor system of the brachial region of the spinal cord of the sheep and the degree of differentiation of individual representative neurons at the end of the premotile and the opening of the motile or reactive period is schematically represented in figure 29 (5) One of the features of the cord that has especial interest for the discussion at hand is the very limited differentiation that has occurred in the internuncial and association neuron systems of the alar and basal laminae If the pyridine silver impregnation methods may be trusted to reveal the true state of the differentiation of these neural elements they are at this stage limited in number and relatively immature Only a few of the commissural cells in the ventralmost part of the basal lamina have acquired dendrites an indication that their axons have arrived at their destination after their headward course in the heterolateral funiculus The more dorsally placed commissural elements in the basal lamina, like those in the alar are unipolar cells The homolateral funicular elements are equally immature and small in number The cell bodies lie predominantly in the region of the junction of the two laminae alar and basal and their axons extend in a ventrolateral direction toward and into the lower half of the lateral funiculus where they turn forward to continue headward at that level or one nearer the ventral root A few of th[illegible]

[illegible]

[illegible] any over the future sub

stantia gelatinosa before turning ventralward, those that spring from fibers more medially placed grow directly downward The most advanced in their growth reach the region in the lower alar lamina that is crossed by the axons and contains the cells of the homolateral funicular fibers All of the collaterals of the dorsal funiculus appear to end in cones of growth, they do not arborize or form any obvious synaptic connections

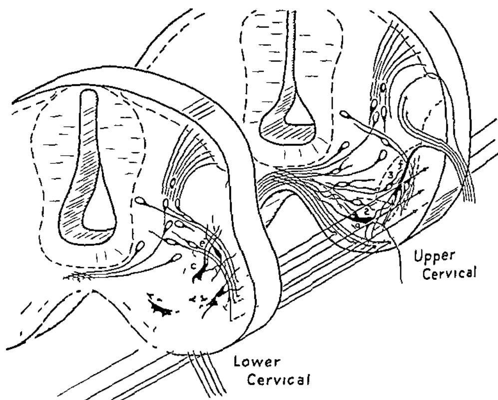


Fig 29 Diagram to illustrate the degree of differentiation of the most advanced neurons of the motor commissural and funicular systems and their pattern of organization in the brachial spinal cord of the sheep embryo of thirty four days the stage in development at which it first reacts to external stimuli

with the associational elements It is important for the problem at hand to recognize that none of the collaterals end anywhere near the motor system or invade the basal lamina at this stage, and further that the collaterals that arise from the dorsal funiculus do so at segmental levels anterior to the region in which the parent fiber enters the cord

With these facts about the organization of the brachial cord at the end of the premotile period in mind, consideration may now be given to the question is the cord organized in a fashion that would, if its motor elements were activated respond in a total pattern in accordance with the views of Coghill or segmentally as Windle has suggested? The develop

ment of the total response in Coghill's sequence follows the stimulation of ... afferent system activating directly or indirectly the longitudinal

which the motor system of the cord can be activated in the ... is not difficult to visualize the activation of the entire motor apparatus, functionally capable of responding, through the synaptic relations of the descending funicular axons and the dendrites extended into the marginal layer after the manner in which similar motor responses appear to be evoked in the adult cords of the cold blooded vertebrates in which the structural organization is so similar to this stage of development in the fetal sheep The relationship of the motor neurons to the muscular system and the funicular system virtually excludes anything but a total response and a total response would appear to be mandatory to activation via any other afferent system that discharged the funicular system of the trunk via the medulla

Consider next the possibility that such an organization could respond in a local or segmental fashion as Windle (22) has proposed The sensory system activated according to Windle is composed of the local segmental afferents The histological evidence set forth here and described in detail elsewhere (Barron, 5) clearly indicates that the collaterals of these afferents do not reach the motor neurons directly at this stage in the development of the sheep cord i e there appear to be no local unsegmental two neuron reflex arcs in the sheep embryo of 34 days Moreover there appears to be no synaptic relationship at this stage of first motility between the dorsal root collaterals and the cells of the commissural and funicular systems

But grant for purposes of discussion that the dorsal root collaterals can, at this stage as Scharpenberg and Windle (19) have suggested, excite the association neurons of the alar lamina and that the association neurons can in turn activate the motor system In these circumstances one would expect that the motor response following excitation of a local afferent nerve—that would from the structure of the brachial plexus, almost certainly contain fibers entering the dorsal roots of two if not three segmental nerves and so be distributed to a wide portion of the cord—should include the muscles of the opposite side as well as the homolateral The former might be expected to respond through the activity of the commissural neurons as they turn forward in the ventral funiculus to engage the dendrites of the ventromedial cell group And this group of cells, as Sprague has shown sends axons to dorsal as well as the ventral primary rami And further the musculature of the limb and trunk of the same side would be activated by the association fibers that pass through the retrodorso

lateral column to excite the distal limb musculature before entering the lateral funiculus to run forward among the dendrites of the neurons of the ventrolateral and dorsolateral motor cell columns whose axons extend to the trunk and proximal limb musculature That is to say, one would expect *on the basis of the organization of the sheep cord at the stage of* earliest fetal activity, that impulses entering the brachial segments via the associated dorsal would make generalized rather than restricted localized responses Or to put this thought in another way the organization of the brachial cord at the stage in which its efferents first respond following stimulation of the trigeminal and the view that the isolated movements of the fore limb, which Barcroft et al (3) observed to follow pressure on the amniotic sac were true reflexes evoked by stimulation of intrinsic limb afferents, are incompatible And their incompatibility in turn casts further doubt upon Windle's contention that the earliest behavior of the sheep—or any mammal—is manifest through isolated reflexes

DIFFERENTIATION OF CORD IN EARLY STAGES OF REACTIVITY

Basic as a knowledge of the organization of the cord at the onset of activity and the forces that wrought it may be to an understanding of the genesis of behavior, more important still is a description of the subsequent pattern of normal differentiation and the circumstances that determine it *As development advances are total patterns fragmented by the growth* of more specific connections or are isolated local arcs amalgamated through the appearance of integrating units? Unfortunately little precise information has been collected with regard the differentiation of the spinal cord at stages beyond that at which the earliest movements occur but the *little that is available is reviewed here more in the hope that it will stimu*late further work along these lines than in the thought that it can contribute materially at this time to the problem of behavioral development

If the pattern of differentiation of the cells of the spinal cord of the sheep and chick at the onset of motility is akin to that of the cold blooded vertebrates *the advances that take place with increasing maturation may* be expected to follow lines not too dissimilar to those that characterize the course of differentiation in phylogeny Cajal (9) points out in the discussion of the evolution of the cord that the plexus in the marginal layer of the cord in the cold blooded vertebrates formed by the funicular fibers *their arborizations and the dendrites of cells in the gray or mantle* layer disappears with the course of evolution The dendrites of the cells of the central gray are almost entirely withdrawn in the cords of adult birds and mammals in contrast the collaterals of the funicular system invade the central gray In general all collaterals increase their length as the motor *and funicular neurons withdraw their dendritic expansions* and are confined to the ventral and dorsal horns with advancing phylogeny

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dorsal funiculi are a bit later. Collaterals from the dorsal funiculi do not *reach the region occupied by the anterior horn cells until the end of the* 8th or the beginning of the 9th day of incubation. Near the end of the 10th day their cones of growth are largely replaced by primitive type endings, and it is of interest in passing that Preyer (18) first observed what he termed local reflex movements of the wing on the eleventh day of incubation! After the arrival of the dorsal root collaterals, the ventral horn cells begin, as they do in the sheep, to resculpture their dendrite pattern—to withdraw them from the funiculi and to extend them into the central gray as well as longitudinally in the cord. These would appear to be structural alterations that would lessen the grossness of the association of the motor system with the funiculi and render it more responsive to the local afferents.

Finally, the observations and considerations presented here indicate that the differentiation of the brachial regions of the spinal cord of the warm blooded vertebrates tends to follow a pattern similar to that known to occur in phylogeny though to be sure that course is not *slavishly* followed. For example, the Rohon Beard cells characteristic of the early Amblystoma cord where they form a special afferent system do not appear to develop in the sheep and the chick and in those cases in which they have been found in the early human cord they may represent phylogenetic rests rather than a functional system (14, 24).

Similarly there is no evidence that the motor connector elements of the Amblystoma cord develop in the sheep. They, like the Rohon Beard cells, would appear to be special features of the larval period that are lost in the amniotes. Similarly, the full development of the marginal plexus appears to be omitted in the warm blooded forms, but a common pattern of differentiation can be traced and one would hesitate to assume that it found no reflection in the pattern of functional development. Aspects of this functional pattern may be expected in turn to be deleted or to appear earlier or later in a given sequence but such variations would not constitute a matter of principal but rather one of detail. It is in this light of such considerations that the alternative hypotheses of Coghill and Windle regarding the genesis of behavior must be viewed and evaluated.

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CHAPTER XII

THE PHYLOGENETIC CONTINUITY OF NEURAL MECHANISMS AS ILLUSTRATED BY THE SPINAL TRACT OF V AND ITS NUCLEUS

ELIZABETH C. CROSBY AND ROBERT E. YOSS[1]

INTRODUCTION

Phylogenetic history frequently sheds light on some of the factors determining the sequence of embryological development of brain centers and tracts and on the probable functional significance of the adult areas. It appears worthwhile, then, to review briefly the phylogenetic development of the primary nuclei of reception for the entering fibers of the cutaneous nerves of the head, together with their central connections and associated gray matter in the light of the recent studies of their embryological history (25, 26) and of their importance for early fetal movements (17, 18, 19, 20).

Before starting the present account it may be well to recall certain facts with which all are undoubtedly familiar but which are nevertheless often lost sight of in discussing the phylogenetic development of various brain structures. These facts may be summed up in the trite statement that we are not dealing with a procession of progressively more highly differentiated forms climbing the trunk of the phylogenetic tree. Rather it is the branches of this hypothetical tree which are occupied by the widely diverse orders of vertebrates. Some of the representatives of these vertebrate orders are near the main trunk, others far out on the branches. In other words, parallel development of brain centers and connections must not be mistaken for direct evolution of such centers or connections from one form to another.

The peripheral components of the cutaneous nerves of the vertebrate head and the centers of reception within the brain for their entering root fibers, together with the secondary connections of these centers, have received wide consideration. Descriptions of them are to be found in practically all accounts of the vertebrate brainstem. To review any considerable portion of this literature is beyond the scope and purpose of the

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present account Throughout the text, reference will be made to previously published descriptions which are particularly pertinent for the discussion Those interested in more extensive reviews should consult the various texts and atlases dealing with the comparative and human anatomy of the brain tem (1, 2, 3 4 36 40, 56, 57, 58, and others) and the special papers concerned with the trigeminal complex such as those of van Valkenburg (48) Woodburne (59), Meesen and Olszewski (31), and Olszewski (35)

The material used in this study is from the Huber Neurological Collection Some of the new series were made possible by a grant from the Horace H Rackham School of Graduate Studies Several of the specimens of tailed amphibians were obtained as a gift from Professor R Humphrey of the University of Buffalo School of Medicine The photomicrographs were made by Mr George J Smith and the drawings by Miss Betty Lou Smith of the Department of Anatomy University of Michigan Miss Shirley Mesnard secretary to the Neuroanatomy Division gave valuable help in the preparation of the manuscript To all of these the authors wish to express their sincere appreciation

PHYLOGENETIC DEVELOPMENT OF THE NUCLEAR PATTERN ASSOCIATED WITH THE TRIGEMINAL NERVE

The two major nuclei of reception of the cutaneous fibers of the trigeminal nerve of vertebrates (3 4 59) are the nucleus of the spinal tract of V and the chief sensory nucleus In 1919 Fuse subdivided the nucleus of the spinal tract of man into three secondary portions on the basis of fiber arrangement Later Olszewski (35) recognized three distinct nuclear masses in the nucleus of the spinal tract of V of macaque and man the nucleus caudalis the nucleus interpolaris and the nucleus oralis He suggested that the name nucleus of the spinal tract (or descending root) of V be dropped in favor of the term spinal trigeminal complex Our own series of macaque and human brains document in all essentials Fuse's and Olszewski's findings Such differences as have been noted are unimportant and may be explainable on minor individual variations or slight modifications in interpretation In 1949 Meesen and Olszewski suggested that in the rabbit the nucleus of the spinal tract of V should be divided into a nucleus caudalis and a nucleus oralis Obviously the term nucleus oralis has not been applied to exactly the same nuclear mass in primates as in subprimates

It appeared probable that if the subdivisions of the nucleus of the spinal tract of V described by Meesen and Olszewski (31) and Olszewski (35) were fundamental it should be possible to trace their gradual evolvement throughout the vertebrate series With this in mind suitably stained material of various mammalian and submammalian brains has been ex

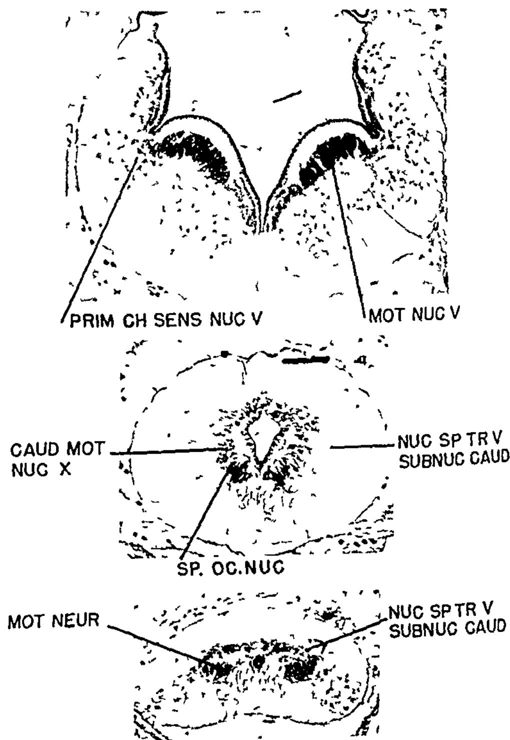


Fig 30 Three photomicrographs through the brainstem and upper cervical spinal cord of the cyclostome Entosphenus appendix Toluidin blue preparation × 60 A Section through the motor nucleus of the trigeminal nerve (MOT NUC V) and the primordial chief sensory

assumed Since the term nucleus of the spinal tract of V is widely accepted and has been employed by Humphrey (28) in her excellent description of the embryonic development of the spinal tract of V, it will be used in the following account, and the names subnucleus caudalis and subnucleus oralis for its major subdivisions where represented in subprimates Further differentiation of subnucleus oralis is indicated if present, by the designations of pars interpolaris and pars rostralis For primates modifying slightly for conformity's sake the terminology of Olszewski, the names of subnucleus caudalis, subnucleus interpolaris and subnucleus rostralis (nucleus oralis of Olszewski) have been used The results from the study of the nuclear pattern in the representative vertebrates may be summarized as follows

Nuclear pattern in cyclostomes

Along the whole course of the spinal tract of V, from its point of entrance into the cyclostome brain at upper rhombencephalic levels to its termination at upper cervical cord levels scattered or intercalated cells are found amid the descending root fibers A cluster of these neurons occurs (possibly as a primordial chief sensory nucleus fig 30) where the nerve enters the brain The scattered cells which are present along the tract scarcely deserve the name of nucleus although undoubtedly they receive impulses by collaterals and perhaps stem fibers of the spinal tract of V At the caudal end of this tract near its entrance into the cord a cluster of cells forms a small poorly circumscribed but nevertheless characteristic subnucleus caudalis (fig 30) This subnucleus lies medial to the tract and passes without sharp transition into the dorsal horn gray of the spinal cord (fig 30)

Nuclear pattern in various fishes

No indication of even a primordial chief sensory nucleus was found in the available series of the brain of the dogfish (Mustelus canis) Woodburne (59) could find no trace of this nucleus in Amia calva In higher fishes the size and differentiation of the trigeminal system differs from form to form and no one description will fit all of them In the brook trout for example a few scattered cells at the level of entrance of the cutaneous trigeminal fibers probably constitute a primordial chief sensory

is a uppermost sp r
caudalis w th the gray of

nucleus, but these cells are not clearly differentiable from the remaining *periventricular gray*. In all of the fish brains examined, *along the spinal* tract of V as it proceeds caudalward, are scattered neurons which are partly intermingled with the fiber fascicles and sometimes lie along their medial border. Since the position of the spinal tract of V varies greatly in different fishes, depending particularly upon the degree of development of other systems such as the lateral line or gustatory (*fig. 39*), the position of the gray associated with the spinal tract will vary likewise with respect to the tract. This primordial nucleus of the spinal tract of V increases slightly in its most caudal portion and in higher fishes becomes continuous with *the medial funicular nucleus* which also receives trigeminal root fibers. The medial funicular nucleus (Herrick, 15) is a specially differentiated *part of the dorsal horn gray (with which the subnucleus caudalis of the* spinal tract of V is closely related). It receives descending trigeminal root *fibers and dorsal root fibers from upper cervical levels.* The medial funicular nucleus, in some fishes at least, receives the descending gustatory tract (14, 15). The emphasis again is on the importance of cervical cord correlations at this phylogenetic level.

Nuclear pattern in amphibians

Turning now to a consideration of the relations in more generalized *types of amphibians*, it becomes evident that there is *little more specialization* in the nuclear gray associated with the spinal tract of V in some of *the tailed amphibians (Amblystoma, Necturus) than in cyclostomes.* At the place of entrance of the trigeminal roots a small area within the periventricular gray (fig. 31A) ventromedial to the sulcus limitans and adjoining the lateral border of the motor V nucleus is *barely differentiable* from the remainder of the morphologically undifferentiated periventricular gray by the slightly larger size of its neurons and the somewhat greater coarseness of the dendrites arising from them. At most it is a very primordial chief sensory nucleus, lacking the characteristic *contour and* certain of the relations significant for this nucleus in higher amphibians. *Along the course of the spinal tract of V are scattered cells and intercalated* among its fibers are small numbers of interstitial neurons. Occasionally these scattered cells congregate into small clusters which are indistinctly separated from the periventricular gray and which lie in relation with the dorsomedial border of the spinal tract of V. Such a small cluster is found at acoustic levels (it was termed the incipience of a sensory trigeminal nucleus by Herrick, 16) and again at vagal and postvagal levels, as both Herrick (16) and Woodburne (59) have described. *Both of these observers* found and the present work confirms the presence of neurons slightly *larger than the periventricular cells* at vagal and slightly smaller at calamus

scriptorius levels It seems probable that the group at calamus levels corresponds to the subnucleus caudalis described for cyclostomes, since it becomes continuous with spinal cord gray (fig 31B)

Frogs have a small chief sensory nucleus, differentiated out of the periventricular gray, lateral and slightly dorsolateral to the motor nucleus of V (fig 32A) It is continuous ventrally and ventrocaudally with the nucleus of the spinal tract of V This latter nucleus extends caudalward, over-

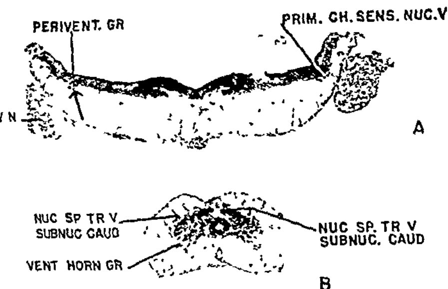


Fig 31 Photomicrographs of toludin blue preparations of the brain and upper spinal cord of Necturus maculosus × 60 A
trance of the trigeminal nerve (V
GR) and the arrow points to the
chief sensory nucleus On the righ
Photomicrograph taken at an up
HORN GR) showing the subnuc of the nucleus of the spinal tract of V (NUC SP TR V SUBNUC CAUD)

lapping the gray of upper cervical cord and gradually disappearing In front of the calamus the nucleus of the spinal tract of V shows an intermingling of slightly larger neurons which contain more deeply staining Nissl substance in the cresyl violet and toludin blue preparations, so that the rostral part of the nucleus has a different cell character than does its caudal portion and may be regarded as a developing subnucleus oralis (fig 32B) As the chief sensory nucleus is approached, the subnucleus oralis becomes somewhat less differentiated The nucleus of the spinal tract of V is somewhat more discrete toward its caudal end (beginning at

nucleus, but these cells are not clearly differentiable from the remaining periventricular gray. In all of the fish brains examined, along the spinal tract of V as it proceeds caudalward, are scattered neurons which are partly intermingled with the fiber fascicles and sometimes lie along their medial border. Since the position of the spinal tract of V varies greatly in different fishes, depending particularly upon the degree of development of other systems such as the lateral line or gustatory (fig. 30), the position of the gray associated with the spinal tract will vary likewise with respect to the tract. This primordial nucleus of the spinal tract of V increases slightly in its most caudal portion and, in higher fishes, becomes continuous with the medial funicular nucleus which also receives trigeminal root fibers. The medial funicular nucleus (Herrick, 15) is a specially differentiated part of the dorsal horn gray (with which the subnucleus caudalis of the spinal tract of V is closely related). It receives descending trigeminal root fibers and dorsal root fibers from upper cervical levels. The medial funicular nucleus in some fishes at least, receives the descending gustatory tract (14, 15). The emphasis again is on the importance of cervical cord correlations at this phylogenetic level.

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about the calamus level) and in this portion of the nucleus the cells are smaller and less specialized in appearance. They constitute a subnucleus caudalis (fig. 32C). There are in general very few intercalated cells in the course of the spinal tract of V in frog. Nearly all the cells have assumed a position medial to the tract to form its typical nucleus. The outline of the nucleus conforms throughout to that of the root fibers.

Nuclear pattern in reptiles

Although there are some differences in the degree of cell specialization and in the size of the nuclei in passing from one reptile to another, in general the cutaneous trigeminal complex in all the reptiles studied shows a well differentiated chief sensory nucleus of intermingled medium sized and smaller cells and a typical nucleus of the spinal tract of V, which conforms to the shape of the root. It can be subdivided into a subnucleus oralis and a subnucleus caudalis. There are some slight indications that in the alligator at least the subnucleus oralis may be separating further into a pars rostralis and a pars interpolaris. Pars rostralis is the less well differentiated portion and in the transverse alligator series at least is kidney shaped at most levels. It extends from the chief sensory nucleus with which it is in continuity spinalward to acoustico facial levels where it is gradually replaced by pars interpolaris. Pars interpolaris, which consists of medium-sized triangular shaped neurons intermingled with smaller spindle shaped cells, is replaced in front of the calamus by the subnucleus caudalis. This subnucleus makes up the rather extensive small celled part of the gray of the cord at upper cervical levels (fig. 42, NUC. SP. TR. V). In the series of reptilian brain material consulted the above pattern is less evident in the turtles and more clear in the snake, the lizard and the alligator.

Nuclear pattern in birds

In birds probably in correlation with the development of more highly specialized tactile terminations (49) there is usually a marked increase in size of the chief sensory nucleus (fig. 33) as compared with that of lower

Fig. 3[illegible] Photomicrographs of three levels through the brain stem and uppermost cervical spinal cord of the frog (Rana catesbeiana). Tolu[illegible] the [illegible]

[illegible] very [illegible] nous from [illegible] tarius present. C. Section through the level of the nucleus of the first spinal nerve (NUC. SP. N. I). This section shows the gradual transition of the small cells of the nucleus of the spinal tract of V (NUC. SP. TR. V. SUBNUC. CAUD.) into the dorsal horn gray.

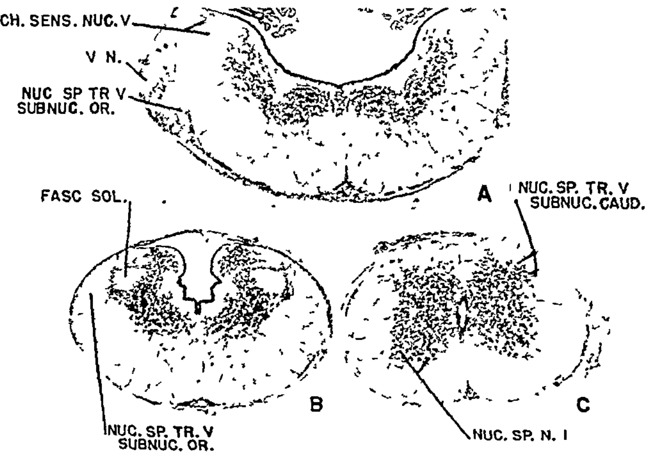

CH. SENS. NUC. V
V N.
NUC SP TR V
SUBNUC. OR.
A
NUC. SP. TR. V
SUBNUC. CAUD.
FASC SOL.
B
C
NUC. SP. TR. V
SUBNUC. OR.
NUC. SP. N. I

Fig 8?

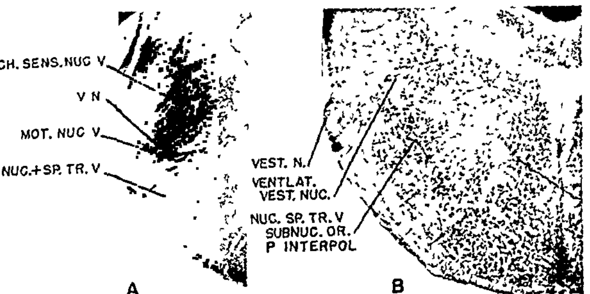


Fig 34 Photomicrographs of the brainstem of the sparrow, *Passer domesticus*. A Section through the level of entrance of the trigeminal nerve (V N) showing its distribution to the chief sensory nucleus of V (CH SENS NUC V). The motor nucleus of the trigeminal nerve (MOT NUC V) and the rostral end of the spinal tract of V and its nucleus (NUC + SP TR V) are shown. Pyridine silver preparation × 25. B The level of the entering vestibular nerve (VEST N) showing the ventrolateral vestibular nucleus (VENTLAT VEST NUC) overriding the subnucleus oralis (NUC SP TR V SUBNUC OR). The area shown represents the pars interpolaris of the subnucleus oralis (P INTERPOL). Toluidin blue preparation × 25

forms and a somewhat more differentiated cell type makes its appearance in this sensory area. There are some variations in degree of development of the nuclear gray from one bird to another but in all the avian material available for study the chief sensory nucleus is well developed. In one respect it differs in its relationships from that of the corresponding nuclei

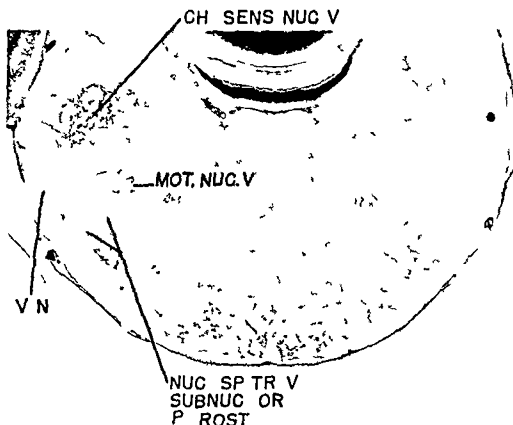


Fig. 33. Photomicrograph of a section through the level of entrance of the trigeminal nerve in the sparrow, Passer domesticus. Toluidin blue preparation. × 25. The well differentiated chief sensory nucleus of V (CH. SENS. NUC. V) and the rostral tip of the small pars rostralis of the spinal nucleus oralis (NUC. SP. TR. V SUBNUC. OR. P. ROST.) are shown. The entering root fibers of the trigeminal nerve (V N) and the motor nucleus of V (MOT. NUC. V) are indicated in the figure.

in reptiles and mammals—it is not continuous with the nucleus of the spinal tract of V in the birds studied. That such a close relationship may exist in some avian forms is quite possible.

The avian nucleus of the spinal tract of V begins at the level of entrance of the trigeminal root and extends caudalward along the inner side of the spinal tract conforming at all levels to the shape of this root (figs. 34 and 35). It overlaps the dorsal horn gray dorsally and dorsomedially at upper

cervical cord levels where it terminates The division of the nucleus of the spinal tract of V into subnucleus oralis and subnucleus caudalis is quite clear There are indications of a beginning differentiation of the subnucleus oralis into a pars rostralis and a pars interpolaris Pars rostralis (fig 33) is the less differentiated portion of the subnucleus extending from the place of entrance of the trigeminal root caudalward to vestibular root levels It contains two types of neurons some with spindle shaped and others with more nearly spherical cell bodies Pars interpolaris (fig 34B) gradually replaces pars rostralis as its characteristic lattice work appearance produced by neurons and intermingled fibers becomes evident The subnucleus caudalis (fig 35) extends from somewhat in front of the calamus region through lower medulla levels into the uppermost cervical levels of the spinal cord In it can be recognized an outermost, small marginal layer a wide gelatinous layer of cells and fibers resembling in appearance the substantia gelatinosa of the spinal cord and a large central portion in which are some larger as well as smaller neurons

Nuclear pattern in subprimate mammals

Practically all modern workers on the mammalian brainstem have recognized a chief sensory nucleus and a nucleus of the spinal tract of V, which is continuous with this chief sensory nucleus and which extends spinalward through the brainstem to cervical cord levels It overlies [illegible]

[illegible] of the nuclear groups related to the termination of cutaneous components of the trigeminal nerve in various mammals depending upon the number and on the specialization of these cutaneous nerve endings in the form under consideration The degree of development of this system is grounded again in the habits of life of the mammal in question such as its manner of eating or its use of nose or whiskers as exploratory organs Thus the nuclear gray associated with tactile components of the trigeminal nerve is relatively very highly developed compared with other brainstem centers in the duck billed platypus (Ornithorhynchus) in the mole and in the bat it is well developed in cat and man The brains of two subprimate forms—those of opossum (not illustrated) and bat have been chosen to represent the differentiation of the chief sensory nucleus of V and the development of the nucleus of the spinal tract of V in subprimate mammals

The rostral tip of the chief sensory nucleus of the trigeminal nerve in the opossum lies just in front of the oral pole of the motor trigeminal nucleus It is surrounded and invaded by entering root fibers and separated from the large-celled motor nucleus as this appears by the main bundles

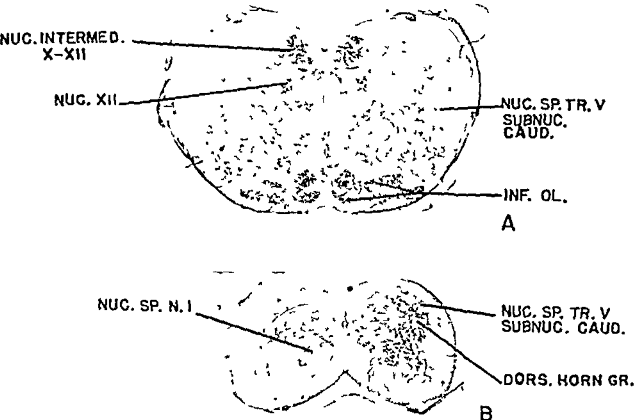


Fig. 35. Photomicrographs of levels through the medulla and uppermost cervical spinal cord of the sparrow, Passer domesticus. These figures are made from the same series as figure 33 and figure 34B. Toluidin blue preparation × 25. A. Section at the level of the nucleus intermedius (NUC. INTERMED. X–XII) and nucleus hypoglossus (NUC. XII). The conspicuous avian inferior olive (INF. OL.) is illustrated in this figure. The figure is designed to show the position of the more rostral portion of subnucleus caudalis (NUC. SP. TR. V SUBNUC. CAUD.). B. Section through the level of the nucleus of the first spinal nerve (NUC. SP. N. I). The well developed caudal portion of the subnucleus caudalis (NUC. SP. TR. V SUBNUC. CAUD.) as it comes into relation with the dorsal horn gray (DORS. HORN GR.) is indicated.

distinctly ventrolateral to a dorsolateral position as the fourth ventricle closes to form the central canal

In the toluidin blue preparations the chief sensory nucleus in the bat (Tadarida mexicana) appears as a mass of medium sized, multangular neurons with deeply staining nuclei and fine well stained Nissl granules The cells are in clusters and sometimes in rows between the trigeminal

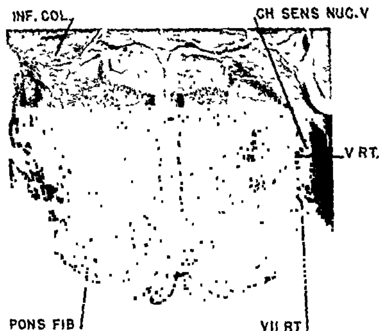


Fig 36 Photomicrograph of the brain of the bat, Tadarida mexicana, at the level of the chief sensory nucleus of the trigeminal nerve (CH SENS NUC V) The root fibers of this

ually cut in an oblique plane so that
is visible and the ventral part of the
ers of the facial nerve (VII RT) also

fascicles which spread around and through the nucleus The chief sensory nucleus (fig 36) has the typical plano-convex contour and lies lateral
the trigeminal root, which
Its rostral tip is not ver
and prominence of th
entrance of the trigeminal roots (some of these ... nucleus at the level of
fibers ... re amid the root
t ... very few within
Ventrocaudally

of the trigeminal nerve It disappears gradually in front of the caudal tip of the motor nucleus It is connected by strands of cells with the nucleus of the spinal tract of V, which appears ventral and ventromedial to it

The chief sensory nucleus of V in the opossum is elongated dorsoventrally (where best developed) being somewhat plano convex in shape with the convex surface laterally However it does not maintain this outline consistently in the available material Its cells are small stellate and small triangular or oval neurons with typical fine Nissl granules Intermingled are some larger, darker staining multipolar neurons All the cells are much smaller than those of the neighboring motor trigeminal nucleus

The nucleus of the spinal tract of V extends from the chief sensory nucleus into upper cervical cord in the opossum in the typical relations Its subnucleus oralis appears ventral to the motor nucleus of V continuous with the chief sensory nucleus and intermingled with the entering trigeminal root fibers At the rostral tip of this subnucleus the cells are rather closely grouped without special arrangement but the nuclear gray soon begins to take on a mesh like appearance the cells forming lines and strands among the fiber bundles The contour of the nucleus conforms laterally to the crescent shape of the spinal tract as it turns caudalward in its course toward the cervical cord Intermingled with and on the medial border of the small triangular to stellate cells which make up the main mass of the subnucleus oralis at these levels are scattered much larger triangular shaped neurons with wide flung dendrites

As it proceeds caudalward the descending root lies medial and ventromedial to the fibers of the acoustic nerve and their nuclei of termination and lateral and dorsolateral to the facial nucleus Farther spinalward both nucleus and root are crossed by glossopharyngeal and then by vagus rootlets Throughout its extent until about the level of the calamus the subnucleus oralis has retained substantially the same character although there are minor variations from level to level Scattered neurons are seen in the spinal tract of V and these increase as the calamus is approached so that a pars gelatinosa becomes quite evident a marginal layer can be recognized and the central part of the nucleus becomes more dense Thus there is a gradual transition into subnucleus caudalis at about obex levels

The subnucleus caudalis extends then from just in front of the obex level into the upper cervical cord where it lies dorsomedial to and then is replaced by dorsal horn gray which it greatly resembles In the opossum this subnucleus caudalis has a morphologic structure very similar to that described for the comparable area in the rabbit by Meesen and Olszewski (31) All three portions—a marginal a gelatinous and a central (or magnocellular part Meesen and Olszewski)—are recognizable Throughout its extent in the medulla the nucleus of the spinal tract of V gradually shifts from a

the chief sensory nucleus becomes continuous with the subnucleus oralis of the nucleus of the spinal tract of V.

Subnucleus oralis (fig. 37A) in the bat consists of small and small to medium sized cells intermingled at some levels with a few deeply stained, multipolar cell bodies which resemble somewhat the multangular neurons of the chief sensory nucleus. Although these neurons are fairly closely spaced, they are intermingled with fiber fascicles (some from the spinal tract of V, others with fibers of passage). The mass follows the contour of the spinal tract of V which encircles it dorsally, laterally and ventrally. The medial tip of the nuclear mass contains fewer cells than does the rest of the nucleus but some of these neurons are fairly large and multipolar. Followed caudally, at facial and acoustic levels, the arrangement of the cells becomes less dense. They are relatively uniform in size and staining—only occasional small fusiform or spindle shaped neurons are seen—and the lattice work arrangement is very fine but is more evident than at the rostral end of the nucleus. The mass itself is relatively large. Some of the strands of cells extend into the spinal tract of V. The condition here is intermediate between that of the monkey in which Olszewski (95) recognized a nucleus interpolaris and a nucleus oralis and that in rabbit and opossum where these two nuclei form an almost common mass which Meesen and Olszewski (81) termed nucleus oralis and the present writers call subnucleus oralis. It would appear that the subnucleus oralis in the bat has a pars rostralis and a pars interpolaris (fig. 37A) which, although not differing greatly from each other, suggest the nuclei (or subnuclei) of the same name seen in man and monkey but are less clearly demarcated.

Subnucleus caudalis appears in front of the obex region, overlapping somewhat subnucleus oralis (fig. 37B). It has a marginal layer, a wide gelatinous part and a narrow central portion in which are occasional large cells. Small oval and small more deeply staining triangular or multangular neurons are intermingled with root fibers. This subnucleus caudalis is relatively very large [illegible]

the [illegible] present shape [illegible]

Fig. 37 [illegible] ... NUC. SENS. NUC. ... [illegible] ... SP. TR. V ... [illegible] ... the region [illegible] ... NUC. SP. TR. V. ... [illegible]

[illegible] ... NUC. CAUD. ... The position of the spinal tract [illegible] ... SP. TR. V. ... [illegible] ... the left side of the figure. INF. CER. PED., inferior cerebellar peduncle; N. XII N., hypoglossal nerve. [illegible]

LAT. VEST. SP. TR. +
LAT. VEST. NUC.
NUC. SP. TR. V
SUBNUC. OR.
P. ROST. TRANS.
TO P. INTERPOL.
GENU VII
SP. TR. V
A

NUC. SP. TR. V
SUBNUC. OR.
P. INTERPOL. TRANS.
TO SUBNUC. CAUD.
XII N.
INF. CER. PED
SP. TR. V
B

Fig 87

However, as Ariens Kappers (1, see also Ariens Kappers, Huber and Crosby 3) pointed out, the response to these stimuli indicates that they are not always disagreeable Endings which elicited such a positive response he classified as gratoreceptive endings

At least as far down in the phylogenetic scale as higher amphibians and reptiles (42) more specialized tactile and pressure endings make their appearance Among submammals, birds have the most highly specialized sensory corpuscles on the head for here appear the corpuscles of Herbst (13) of Grandex or Grandry Merkel (Grandry, 11, Merkel 32, 33, Cajal, 7) and of Key Retzius (29) In mammals a variety of nerve terminations subserving tactile and light pressure occurs in addition to the free sensory endings Over the trigeminal distribution the tactile endings range from the relatively simple tactile menisci through the elaborately coiled endings around the hairs to the highly specialized Meissner corpuscles found on the lips and other limited regions of the head There are also special temperature endings in mammals associated with the more epicritic types of temperature appreciation

Peripheral roots

In all vertebrates the cutaneous components of the trigeminal nerve co... in over ... mandib... cells are ... large unipolar neurons although in some lower forms (as for example in cyclostomes) bipolar cells occur as they do during human embryological development Between the brain and the ganglion, and also within the brain the maxillo mandibular bundles are often particularly intimately associated with each other and differentiable from the fascicles of the ophthalmic division The ease with which they may be separated from each other differs with the form under consideration The relative positions of the two subdivisions of the trigeminal root through a long series of vertebrates have been reported upon by van Valkenburg (48 see also Ariens Kappers 1 Ariens Kappers et al ...

However, ... performed on human patients skilled neurosurgeons have often been able to distinguish between the maxillo mandibular and the ophthalmic divisions It is more difficult to distinguish these two divisions in the amphibian reptilian and ...

passes over directly into the less widespread dorsal horn gray which it greatly resembles

Nuclear pattern in primates

The chief sensory nucleus of V is generally recognized in primates The nucleus of the spinal tract of V has been very well described by Olszewski (35) and his terminology discussed earlier in this paper (page 175) No further account is required

PHYLOGENETIC DISTRIBUTION OF THE CUTANEOUS TRIGEMINAL ROOT FIBERS

Nerve terminations

The appearance of an increasingly wider range of nerve terminations through the ascending vertebrate scale is the morphologic indication of the higher organisms responses to a wider environmental range Thus differentiated tactile and proprioceptive nerve endings comparable to although not completely like those of mammals seem to appear phylogenetically at about the time that the vertebrate *loses* his lateral line canals and exchanges his mode of life from that of a water to that of a land animal Obviously he is thus better fitted to respond to the wider range of stimuli which he will meet in this new environment In the ascending scale of vertebrates through submammals and also from lower to higher mammals the number sometimes the complexity and often the distribution of the more specialized endings of cutaneous nerves (like the development of the special senses) reflect to some degree the habits of life and the special demands which his surroundings make upon an animal

Phylogenetically the oldest type and one of the simplest of nerve terminations appears to be the greatly branched and rebranched and unencapsulated ending which has usually been termed a free sensory ending (21 39 and many others) Whether these are true endings whether *they* form an anastomosing unmedullated network as Vitali (49) and Stephanelli (45 46) believed or whether they pass over into ultraterminal fibrils of the sort described by *Boeke* (5) and by Meyling (34) is not a matter *for* discussion here Such simple sensory endings are the only terminations in the skin of the lowliest vertebrates (for example Retzius 38 for lampreys) They also occur widely *in higher forms* (39) *in general on surfaces or in* areas of head and body which are sensitive to extremes of temperature to

Throughout vertebrates such
have not only impulses set up
alized or dyscritic (37) type of

tactile sensibility and to serve extremes of temperature Sherrington (44) felt that such *endings were primarily nocireceptors* The major function of these endings quite certainly is the protection of the organism from harm

However, as Ariëns Kappers (1, see also Ariëns Kappers, Huber and Crosby 3) pointed out the response to these stimuli indicates that they are not always disagreeable Endings which elicited such a positive response he classified as gratoreceptive endings

At least as far down in the phylogenetic scale as higher amphibians and reptiles (49) more specialized tactile and pressure endings make their appearance Among submammals birds have the most highly specialized sensory corpuscles on the head for here appear the corpuscles of Herbst (13) of Grandry or Grandry Merkel (Grandry, 11, Merkel 32 33, Cajal 7) and of Key Retzius (29) In mammals a variety of nerve terminations subserving tactile and light pressure occurs in addition to the free sensory endings Over the trigeminal distribution the tactile *endings range from the* relatively simple tactile menisci through the elaborately coiled endings around the hairs to the highly specialized Meissner corpuscles found on the lips and other limited regions of the head There are also special temperature endings in mammals associated with the more epicritic types of temperature appreciation

Peripheral roots

In all vertebrates the cut*aneous components* of the trigeminal nerve come in over the three *divisions* of the nerve—the ophthalmic, the maxillary the mandibular—with *their origin* in ganglion cells on the root Such ganglion cells are characteristically large unipolar neurons although in some lower forms (as for example in cyclostomes) bipolar cells occur as they do during human embryo*logical dev*elopment Between the brain and the *ganglion* and also *within* the brain the maxillo *mandibular* bundles are often particularly intimately associated with each other and differentiable from the fascicles of the ophthalmic *division* The ease with which they may be separated from each other *differs with the* form under consideration The relative positions of the two subdivisions of the trigeminal root through a long series of vertebrates have been reported upon by van Valkenburg (48 see also Ariëns Kappers 1 Ariëns Kappers et al 3) The ophthalmic portion can be seen to enter the brain slightly cen[illegible]

[illegible] neuro[illegible] have often been able to distinguish between the maxillo mandibular and the ophthalmic divisions [illegible]

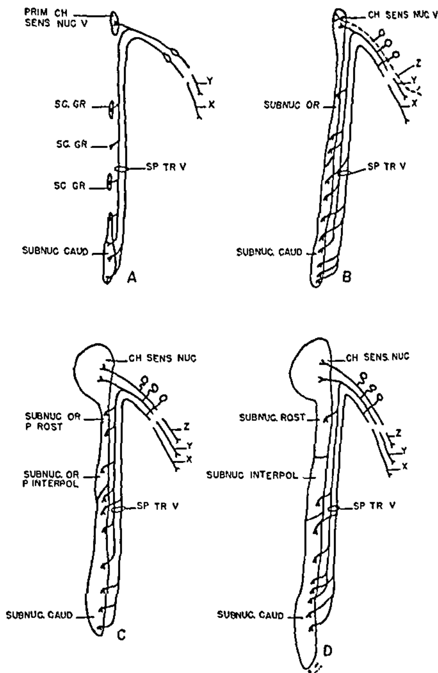


Fig 88. Four diagrams to illustrate the progressive differentiation of the nuclear gray associated with entering cutaneous trigeminal roots and the distribution of the unbranched descending (X), bifurcating (Y) and unbranched ascending (Z) root fibers to the special portions of this nuclear gray. A, tailed amphibian; B, frog; C, bird or subprimate such as cat; D, primate. CH SENS NUC V, chief sensory nucleus of V; PRIM CH SENS NUC V, primordial chief sensory nucleus of V; SP TR V, spinal tract of V; SC GR, scattered gray along spinal tract of V; SUBNUC CAUD, *subnucleus caudalis of nucleus of spinal tract of V*,

portions of the trigeminal nerve have convinced the present writers that in these forms the ophthalmic fibers enter ventral and slightly cephalic to the other divisions of this nerve

Central distribution of root fibers of V

After the cutaneous fibers of the trigeminal nerve have entered the brainstem some of them turn directly caudalward in the spinal tract of V (fig 38) probably in all forms from cyclostomes (Ammocoetes Tretjakoff, 47 various submammals Woodburne 59, pig Windle, 55) to mammals, presumably including man Other fibers bifurcate at their entrance (fig 38) one branch entering the spinal tract of V the other passing either to a special region of the periventricular gray or, as it develops to the better differentiated chief sensory nucleus of V In the available material of cyclostomes, the branches to the periventricular gray are few in number and have the general appearance of collaterals Such branches become more prominent concomitantly with the development of a chief sensory nucleus in higher submammals (59) In addition to these non bifurcating descending fibers and the bifurcating fibers in the silver material of the brain of the lizard (Anolis carolinensis) and in a similarly prepared series of the sparrow brain a few apparently unbranched larger fibers (fig 38C) entering as trigeminal root fibers could be traced to the chief sensory nucleus Possibly such fibers are present in higher amphibians (fig 38B broken line) but could not be demonstrated in the available series The presence of these three types (fig 38 C and D)—unbranched descending bifurcating and non bifurcating ascending fibers—have been beautifully demonstrated by Windle (55) in the fetal pig His interpretation of the functional significance of these fibers is well borne out by their phylogenetic history The non bifurcating descending group (fig 38) present throughout the vertebrate series—and presumably terminating peripherally in free sensory endings—subserves impulses set up by painful stimuli as Windle suggested but probably also those aroused by the grossest temperature stimuli (hot and cold) They are present in all vertebrates The bifurcating fibers (fig 38) [illegible]

[illegible] means by which impulses set up by the most discriminatory types of tactile stimuli are relayed to the chief sensory nucleus These are present only in higher submammals and mam

SUBNUC INT
OR
nucle
SUB [illegible] sub nucleus [illegible] tract of V

mals Whether impulses permitting recognition of warm and cool (as contrasted with hot and cold) are relayed over bifurcating root fibers (which seems more probable) or non bifurcating ascending fibers is as yet uncertain Such modalities are present only in higher forms

In many vertebrates (frog Woodburne, 59, various reptiles Huber and Crosby, 22, Weston, 54, and others, sparrow, Huber and Crosby, 23 Sanders, 41, Woodburne 59 rabbit, Woodburne, 59) direct trigeminal root fibers have been traced to the cerebellum Such connections have not been demonstrated with certainty in man The material available does not permit their clear recognition in cyclostomes or fishes

Addition of components of VII, IX and X to spinal tract of V

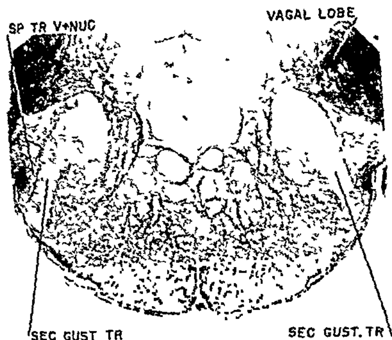
In many vertebrates a cutaneous sensory component occurs in the VII IX and X cranial nerves This component is almost invariably present in X, usually occurs in VII but has not been demonstrated in IX in some vertebrates (for example in some of the fishes amphibians reptiles and birds) in which it has been sought (3) Since it is very small when present failure to demonstrate it does not provide adequate evidence of its non existence It does occur (along with cutaneous components in VII and X) in many mammals including man as Larsell and Fenton (30) and others have pointed out

When present the cutaneous components of VII IX and X join the spinal tract of V in representatives of all the vertebrate orders from cyclostomes to man The sensory roots of IX and X usually cross the spinal tract of V in their course and contribute fibers to it as they pass Where they can be traced such fibers appear to join the dorsal aspect of the ophthalmic division in various vertebrates—for example in the larval form of Ammocoetes (47) and in certain of the fishes where there is sufficient differentiation between the ophthalmic and maxillo mandibular divisions of the spinal root or some especially favorable plane of section permits identification Humphrey (26) believes that they join the spinal tract of V between the maxillo mandibular and the ophthalmic divisions in the human embryo Within the tract they descend to terminate in subnucleus caudalis of the spinal tract of V along with fibers of the trigeminal carrying impulses set up by painful and gross tactile stimuli and by extremes of temperature (hot and cold) Probably the most convincing evidence for this termination in man is the insensibility of the ear to painful stimuli following trigeminal tractotomies at lowermost brainstem levels

Relative position of ophthalmic and maxillo mandibular divisions in spinal tract of V

In these days of trigeminal tractotomies the question of the relative positions and the spinal extents of the maxillo mandibular and the oph

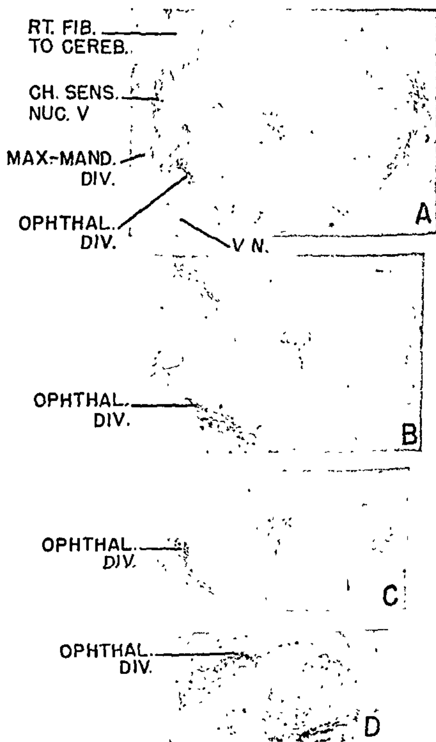
thalmic divisions of the spinal tract of V is a matter of some concern Humphrey (25, 26) has discussed the evidence for a more dorsal position of the maxillo mandibular fibers and a more ventral location of those of the ophthalmic division for mammals in general and especially for the human embryo In a series of submammalian and mammalian forms, van Valkenburg (48) ascribed similar dorsoventral relations to the maxillo mandibular division in most forms He pointed out that in fishes, variations in position occur due to the differences in development of other systems (such as



F g 39 Photomicrograph of a section through the brain of the carp Cyprinus carpio to sl w the pos t n of the sp al tract of V ar d its n u l us (SP TR V + NUC) in relation to the seco l ry gu tatory tr et (SEC GUST TR) at vagal lobe levels Pyri l e s lver preparat on X 25

gustatory and lateral line) in the various forms (ee also fig 39) Sometimes, as in Lophius (3 48) they may be rather widely separated These variations in relations were documented by Woodburne (59) for several fishes (carp brock trout salmon) and are easily demonstrable in the material available in the Huber Collection (see fig 39)

In spite of the evidence for a dorsal pos t o ... and a ... and m ...



F... 10. Photomicrographs of selected levels from the brainstem of a chicken, Gallus domes

their demonstration in certain selected submammalian and mammalian forms.

Section of ophthalmic fibers of the trigeminal complex at their point of entrance to the brainstem was carried out on an adult chicken under sodium pentothal anesthesia. The wound was closed and the chicken kept alive for 10 days. During that time it was tested for loss of sensibility. There was definite marked diminution in response to painful stimuli over the distribution of the ophthalmic fibers and some motor difficulty in eating. Then the animal was sacrificed and the brain removed and prepared according to the Marchi technique. Most of the ophthalmic fibers show degeneration (though a few of them may have been spared). The maxillo-mandibular component exhibits no signs of involvement but there are some degenerated fascicles in the motor root. A few degenerated fibers can be traced to the chief sensory nucleus and, less clearly, to the cerebellum (fig. 40A). At the place of entrance of the trigeminal fibers and caudal to this level the ophthalmic fibers (fig. 40A) are medial and slightly ventromedial in the spinal tract of V. This position is due in part to the great development of vestibular centers in many avian forms. Such centers lie dorsal and dorsomedial to the nucleus of the spinal tract of V at and near the level of entrance of vestibular fibers. Farther spinalward the ophthalmic division becomes more nearly ventral to the maxillo-mandibular portion (fig. 40 B and C). As cord levels are approached, the spinal tract of V ascends dorsally, together with its subnucleus caudalis, to lie in a dorsal and ultimately to extend into a dorsomedial position (fig. 40D) in intimate relation to the dorsal horn gray. At this latter level only a very few (if any) of the maxillo-mandibular fibers remain in the chicken.

The evidence for a dorsoventral relation of the maxillo-mandibular and the ophthalmic divisions of the mammalian spinal tract of V are well illustrated in a series of Marchi preparations of the brainstem of a macaque (Macaca mulatta) in which the maxillo-mandibular division of the trigeminal had been cut proximal to the semilunar ganglion (fig. 41). This operation was performed by the neurosurgeon Dr. Charles Wilson and the material prepared in the Neuroanatomical Laboratory at Michigan.

Distribution and extent of the spinal tract of V

Along the course of the spinal tract of V, fibers (often in the form of collaterals) are given off to come into relation with the neurons asso-

geminal root. B, Section near the transition from pons to medulla. C, Level slightly in front of the calamus scriptorius. D, Section through uppermost spinal cord levels. CH SENS NUC V, chief sensory nucleus of V; MAX MAND DIV, maxillo-mandibular division of spinal tract of V; OPHTHAL DIV, ophthalmic division; RT FIB TO CEREB, root fibers to cerebellum; V N, trigeminal nerve.

ciated with the root. In cyclostomes, fishes and lower amphibians such fibers are relatively few in number, as is to be expected where the nuclear gray along the tract is so minimal in amount. They appear to be more numerous from the maxillo-mandibular than from the ophthalmic portion

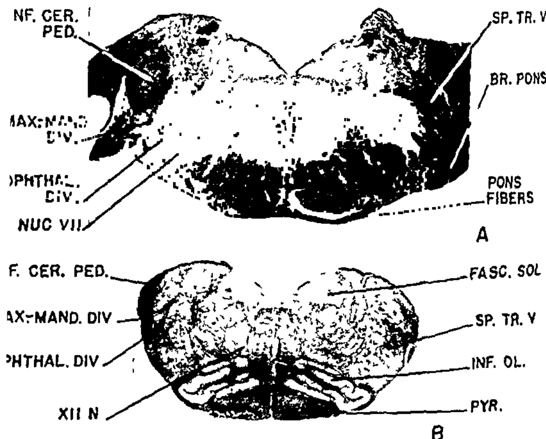


Fig 41 Photomicrographs of two levels through the brainstem of the monkey, Macaca mulatta, *showing the degenerated fibers of the maxillo mandibular division of the spinal tract* of V Weil preparation × 5 A, Section through the lower third of the pons, at the level of the facial nucleus B, Section through the medulla in front of the calamus scriptorius and through the level of the hypoglossal nerve BR PONS brachium pontis, FASC SOL fasciculus solitarius, INF CER PED inferior cerebellar peduncle, MAX MAND DIV *maxillo mandibular* division of the spinal tract of V, NUC VII facial nucleus, OPHTHAL DIV ophthalmic division of the spinal tract of V, PYR pyramid, SP TR V spinal tract of V, XII N hypoglossal nerve

of the spinal tract of V (although this may be merely a staining artifact) The maxillo-mandibular *fibers terminate more particularly in the rostral* end of the subnucleus caudalis in these lower forms (see also van Valkenburg, 48, and *Woodburne, 59*).

In some fishes, at least, the fascicles of the spinal tract of V reach the

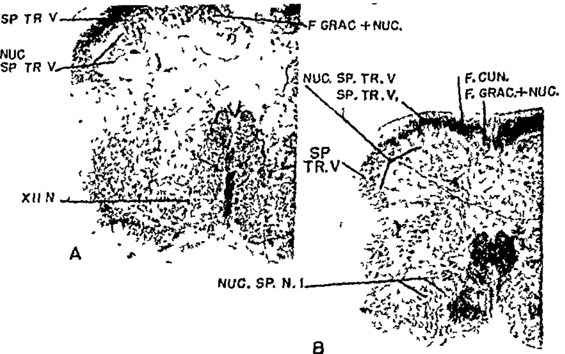


Fig 42 Photomicrographs of sections through the lowermost medulla and upper spinal cord levels of the alligator, *Alligator mississippiensis*. *Iron hematoxylin preparation* × 23. Both of these sections are designed to show the large size of the spinal tract of V at these levels. Note also the small fasciculus cuneatus and fasciculus gracilis and their associated nuclei. F CUN fasciculus cuneatus, F CUN + NUC fasciculus cuneatus plus nucleus cuneatus, F GRAC + NUC fasciculus gracilis plus nucleus gracilis, NUC SP N I nucleus of the first spinal nerve, NUC SP TR V nucleus of the spinal tract of V, SP TR V spinal tract of V, XII N hypoglossal nerve

ciated with the root In cyclostomes, fishes and lower amphibians such fibers are relatively few in number, as is to be expected where the nuclear gray along the tract is so minimal in amount They appear to be more numerous from the maxillo mandibular than from the ophthalmic portion

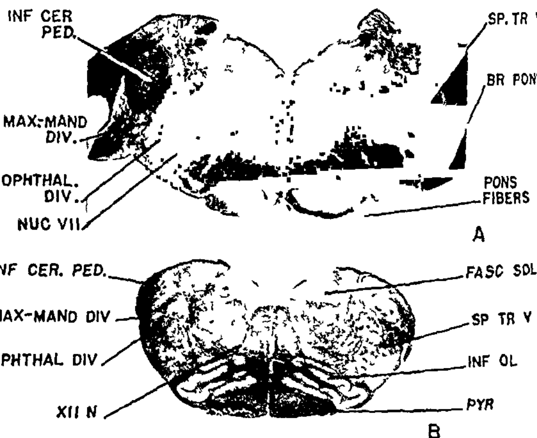


Fig 41 Photomicrographs of two levels through the brainstem of the monkey Macaca mulatta showing the degenerated fibers of the maxillo mandibular division of the spinal tract of V Weil preparation × 5 A Section through the lower third of the pons at the level of the facial nucleus B Section through the medulla in front of the calamus scriptorius and through the level of the hypoglossal nerve BR PONS brachium pontis FASC SOL fasciculus solitarius INF CER PED inferior cerebellar peduncle MAX MAND DIV maxillo mandibular *division of the spinal tract of V NUC VII facial nucleus* OPHTHAL DIV ophthalmic division of the spinal tract of V PYR pyramid SP TR V spinal tract *of V XII N hypoglossal nerve*

of the spinal tract of V *(although this may be merely a staining artifact)* The maxillo mandibular fibers terminate more particularly in the rostral end of the subnucleus caudalis in these *lower forms (see also van Valkenburg* 48, and Woodburne 59)

In some fishes, at least, the fascicles of the spinal tract of V reach the

medial funicular nucleus of the same and also the opposite side (after crossing in the inferior commissure) In frogs Wallenberg (53) traced them to the lumbar enlargement of the same and the opposite side, the crossing occurring at calamus levels The material available does not permit documentation of Wallenberg's results In the alligator (fig 49), the spinal tract of V is still very large at cervical levels It extends beyond C2 in birds and at least into the third segment of the cervical cord in the macaque In reptiles and birds many ophthalmic fibers distribute at cord levels However in the alligator, at least, and in the sparrow and the dove (and perhaps in other birds) maxillo mandibular fibers are also present at C2 None of the materials studied was favorable for determining the exact caudal extent of the spinal tract of V

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fibers ending at upper levels of the nucleus increases and such distribution becomes more marked in mammals In many mammals the maxillo mandibular fibers appear to end particularly in lower medulla and uppermost cord levels but some fascicles may extend to the lowermost level (about C4) of the spinal tract of V as Dejerine (9) thought to be the case for man Some fascicles of this division are still present at the beginning of C2 in a human series of adult brainstem and cord at our disposal

PHYLOGENETIC DEVELOPMENT OF THE SECONDARY TRIGEMINAL CONNECTIONS

It is not our purpose to discuss the secondary interrelations of the cutaneous trigeminal complex in detail but there are certain facts with regard to such relations which serve to explain the significance of the nuclear pattern of the primary centers for reception of trigeminal fibers Those will be mentioned briefly In general these pertinent relations are of two sorts a) secondary reflex connections and b) projection paths to higher centers

In all vertebrates but on the whole in increasing number from lower to

dorsal thalamic nucleus ventralis DORS SEC ASC TR V dorsal secondary ascending tract of V CEN COR general cortex HEMISPH hemisphere HYPERSTR hyperstriatum NEOSTR neostriatum NUC SP TR V SUBNUC CAUD nucleus of spinal tract [illegible] nucleus caudalis NUC SP TR V SUBNUC [illegible]
[illegible] subnucleus interpolaris NUC SP TR [illegible]
[illegible] nucleus oralis NUC SP TR V SUBNUC [illegible]
[illegible] ventralis PALEOSTR paleostriatum [illegible]
sensory nucleus of V SENS V sensory [illegible]
SP C spinal cord SUP COL [illegible]
THAL STR TR thalamo-striat[illegible]
SEC ASC TR V ventral secon[illegible]

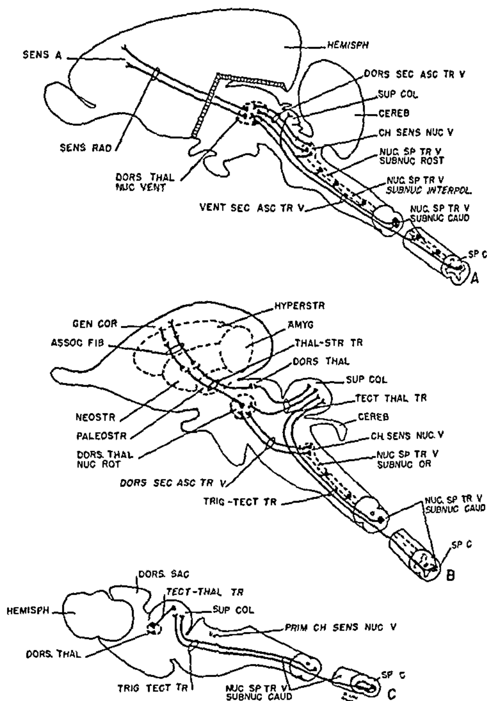


Fig 43 Diagrams showing the ascending systems from the nuclear gray associated with the sensory trigeminal fibers in a cyclostome (C) a reptile (B) and a mammal (A) AMYG amygdala, ASSOC FIB association fibers CEREB cerebellum CH SENS NUC V chief sensory nucleus of V, DORS SAC dorsal sac DORS THAL dorsal thalamus DORS THAL NUC ROT dorsal thalamus nucleus rotundus, DORS THAL NUC VENT

Kappers Huber and Crosby, 3) In birds and reptiles they terminate in nucleus rotundus Observers (23) have considered a possible pathway from the developing avian nucleus gracilis and nucleus cuneatus to higher centers including the contralateral nucleus rotundus This forerunner of the medial lemniscus is probably also present in reptiles Trigemino thalamic bundles often termed the dorsal secondary ascending tract of V (fig 49A), have been demonstrated in experimental material following destruction of the chief sensory nucleus of mammals (52) including primates (30) They end in the nucleus ventralis posterior pars medialis of the dorsal thalamus

DISCUSSION

Having briefly reviewed the gradual development of the nuclear complex associated with the cutaneous fibers of the V, VII, IX and X cranial nerves and the variations in branching, distribution, and extent of their cutaneous root fibers a correlation of the various facts may now be attempted It is obvious that in the lower more generalized types of vertebrates—as cyclostomes tailed amphibians and apparently, various fishes—the chief sensory nucleus and the rostral end (subnucleus oralis) of the nucleus of the spinal tract of V show no real nuclear differentiation but are represented by intercalated neurons in the root or in the spinal tract of V or by scattered cells along this tract (fig 38A) The best developed nuclear mass associated with trigeminal root fibers in such lowly vertebrates is the caudal portion of the nucleus of the spinal tract of V (subnucleus caudalis) At the termination of the spinal tract of V in the cord in some fishes there is a specially differentiated nuclear gray (the medial funicular nucleus) where the impulses relayed by the terminating fibers of V are related to those brought in over cervical dorsal roots and descending gustatory fibers (3, 15 16) The typical peripheral nerve terminations on the cutaneous trigeminal fibers in all these lower vertebrates are free sensory endings—the type which is stimulated by painful and gross tactile stimuli and by extremes of temperature Such types of impulses are projected primarily on the caudal end (subnucleus caudalis) of the nucleus of the spinal tract of V These connections once established remain throughout the vertebrate phylum From this caudal end (subnucleus caudalis) of the nucleus of the spinal tract of V relay is made to the tectum of all [illegible]

[illegible] IX and X cranial nerves since such tractotomies section the spinal tract of V before its termination at lower medulla and upper cord (1–4C) levels and so block the path into consciousness It must be remembered that trigeminal tractotomies do not

higher forms, there are short fascicles interconnecting the gray associated with the spinal tract of V with the motor and the reticular centers of the brainstem. Such secondary reflex connections are very limited indeed in the more generalized forms (as cyclostomes and tailed amphibians) where obviously, if one is to decide on the basis of fiber distribution, the main function is a discharge to upper cord levels for connections by intercalated neurons, with motor centers of the spinal cord [see accounts of Humphrey (25, 26) for human embryos]. In higher submammals and in mammals reflex connections at brainstem levels appear to increase.

Secondary connections of afferent trigeminal centers with higher brain levels have been reported upon by many observers. Among these may be mentioned Woodburne (59, Entosphenus), Johnston (28, Petromyzon), Tretjakoff (47, Ammocoetes), Jansen (27, Myxine glutinosa), Burr (6, Orthagoriscus mola), Woodburne (59, carp), Herrick (16, tailed amphibians), Woodburne (59, tailless amphibians), Huber and Crosby (22, 24, various reptiles), Wallenberg (51, dove), Schroeder (43, chicken), Huber and Crosby (23, sparrow), Wallenberg (52) and Walker (50, primates).

In representative vertebrates from cyclostomes to man, secondary trigemino-tectal paths have been described. These are small in lower vertebrates; they probably reach their maximum importance in reptiles and birds, where impulses carried by them may be relayed to the thalamus over tecto-thalamic paths (Huber and Crosby, 22, 24; Craigie, 8; and later, and others); they decrease proportionately in mammalian forms. In lower vertebrates these trigemino-tectal fibers (fig. 43C) arise chiefly from the subnucleus caudalis of the nucleus of the spinal tract V. As a subnucleus oralis becomes clearly differentiated in higher submammals the ascending systems correspondingly increase (fig. 43B). Certainly in mammals and higher submammals the tectum is by-passed by an increasing number of the ascending secondary trigeminal paths so that the system becomes progressively more and more a trigemino-thalamic rather than a trigemino-tectal system (fig. 43A). Yet part of the fibers—probably more particularly those from subnucleus caudalis—still retain trigemino-tectal relations (fig. 43, A and B). Thus the ventral secondary ascending tract of V of primates (including man) carries, dominantly, trigemino-thalamic fibers but has also trigemino-tectal fascicles.

With the gradual elaboration of the chief sensory nucleus of V in higher subprimates new ascending trigemino-thalamic bundles appear (fig. 43B). These bundles, which decussate in part (usually slightly rostral to the trigeminal level), have been described for certain submammalian forms by various observers (Wallenberg, 51; Huber and Crosby, 23, in the dove as a quinto-frontal tract, and Woodburne, 59, in the lizard Anolis) as the forerunner of the dorsal secondary ascending tract of V; see also Ariëns

cutaneous branches of V, VII, IX and X cranial nerves. The operation was performed by Dr. Edgar Kahn, Director of the Neurosurgical Division at University Hospital, Ann Arbor, with whose permission it is mentioned here. The patient made an uneventful recovery. She showed a complete loss of pain over the expected area except for a small region of sparing on the upper lip. She recognized hot and cold as warm and cool, and readily identified warm and cool stimuli correctly over the area insensitive to pain. The various tests carried out to establish these facts, with their documentation in other cases, if possible, are to be reported by Dr. Terpin, Resident on the Neurosurgical Staff at University Hospital.

Evidently the correct recognition of gross hot and cold stimuli in man depends on intact connections of the spinal tract of V with the caudalmost portion of the nucleus of this tract. However, the evidence at present available indicates that the appreciation of warm and cool—that is, of epicritic types of temperature sensibility—does not depend on the caudal part of the gray associated with the spinal tract of V. This evidence is insufficient at present to determine which portion associated with more rostrally terminating cutaneous root fibers is concerned with receiving impulses set up by such stimuli. It is suggested that fibers related to these modalities (warm and cool) may end in the most rostral part of the nucleus of the spinal tract of V—the so-called pars rostralis of the subnucleus oralis—since this is differentiated as a distinct nuclear group only in higher mammalian forms. However, this is an opinion—not a fact. Perhaps the next step should be to test those cases with thrombosis of the posterior inferior cerebellar artery which do not show pontine involvement in order to determine whether or not the appreciation of warm and cool stimuli is still intact. If these modalities were spared, evidence would be afforded for their projection to gray associated with the trigeminal root above the vestibular level.

The most epicritic type of tactile sensibility appears to be projected to the chief sensory nucleus of V, the somewhat less specialized types of tactile sensibility both to the chief sensory nucleus and to the subnucleus oralis of the nucleus of the spinal root of V. As was stated before, it is probable that only general or gross tactile sensations reach the ...

... both the lower vertebrates and the human embryo this pattern provides primarily the morphologic basis for upper cord reflexes in response to stimulation of the head. In higher ... exist in a more varied ... the trigeminal complex ... and central and not only at brainstem but at thalamic and ultimately at cortical levels (fig 434). It gives the morpho

prove that reflexes may not be initiated from more rostral levels of the nucleus of the spinal tract of V. The terminations of a few collateral fibers along the whole course of this spinal tract in lower vertebrates and very *sparse connections from these cells to motor centers suggest that such* reflexes may occur, although to a limited extent above spinal cord level. Nevertheless it seems fairly certain that the major distribution of the entering cutaneous root fibers of the cranial nerves to the caudal portions of the nucleus of the spinal tract of V in lower vertebrates is to further connections with motor centers of the cord and to permit body responses to head stimulation in these forms as in early developmental stages of the human embryo (25, 26). The relatively more rostral termination of maxillo-mandibular fibers than of ophthalmic fibers in the subnucleus caudalis in lower forms (which has been documented by various observers) suggests *that fibers around the mouth may terminate above the level of ending of* the other fascicles of the spinal tract, but still within the most caudal portion of the nucleus of the spinal tract of V. That such a condition persists through mammals into man Dejerine (9) appears to have believed. It may also be indicated in the occasional case in which the trigeminal tractotomy has been carried out very near the transition of brainstem to spinal cord and in which the patient then shows some slight sparing around the lips *(especially the upper lip), although the inside of the mouth and the face* including the external ear and external auditory canal may be entirely insensitive to pin prick. However, the question always arises as to the possibility of only a partial tractotomy and cannot be settled conclusively to the satisfaction of all from the evidence at present available.

Another question of some interest concerns the possible distribution of other than painful modalities to the subnucleus caudalis of the nucleus of the spinal tract of V. *It is probable that general sensations of touch—of* protopathic grade and set up by stimulation of free sensory endings, reach the most caudal gray of the nucleus of the spinal tract of V. However, the present observers know of no real evidence that such is the case, except the very poor development in lower forms (which nevertheless respond to gross tactile stimuli) of all of the nuclear gray associated with the spinal tract of V, except that along its most caudal extent.

It seems probable also that impulses set up by the extremes of temperature such as ice water or hot water (or their equivalents) are also relayed to the most caudal part (subnucleus caudalis) of the nucleus of the spinal tract of V. That this relation is maintained throughout the vertebrate series to man is suggested by the report of Groff and Levy (12) and by the following case history.

A middle-aged woman with a slowly developing metastatic tumor of the lower jaw was admitted to a trigeminal tractotomy for relief of intractable pain over the distribution of th

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logic basis for the physiological responses of such animals to more highly specialized types of cutaneous sensibility. Curiously enough the nervous system does not develop level by level in a series of progressively more highly differentiated forms but apparently concomitantly at several levels —peripheral, brainstem, thalamic—in the same form. This practically simultaneous differentiation at several levels of the nervous system is one of the most intriguing and most difficult problems facing the comparative neurologist

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CHAPTER XIII

THE INHERITANCE AND DEVELOPMENT OF INTELLIGENCE

WILLIAM R. THOMPSON[1]

INTRODUCTION

The title of this paper implies several major questions which will be discussed in turn. First, the importance of heredity in determining intellectual ability; secondly, the extent to which it can be altered by environmental factors; and thirdly, the nature of the genetic mechanism governing its inheritance. The subsidiary problem of the development of intelligence, also in the title, is important, as will be shown later, to the second of these questions.

Now all three imply a fourth and perhaps more basic problem which will be discussed first, namely, the nature of the trait called intelligence.

While it is a term that finds common usage in the language of the layman, it is one that the psychologist finds very hard to define to his satisfaction. One of the great difficulties of the behavioral sciences is that many of their symbols are taken directly from popular speech and thus lack the singleness of meaning that should characterize the language of science. Accordingly, with the rise of the mental testing movement around the end of the last century, defining intelligence became quite a popular pastime among psychologists and continued to be so for a good number of years. Ebbinghaus, for example, defined it as the ability to elaborate a whole into its worth and meaning by means of combination, correction and completion of numerous kindred relationships. Binet, a patriarch in the field, believed that intelligence involved the ability to select and maintain a definite psychic direction, the ability to make adaptations leading to a desired end, and the ability to criticize one's own behavior. Spearman, the father of factor analysis, reduced it to the ability to educe relations and correlates. Thorndike called it simply the power of making good responses from the standpoint of truth or fact, while Terman regarded it more specifically as the ability to abstract. Recently, Cyril Burt, emphasizing its inherited component, defined intelligence as "innate general intellectual efficiency" (11).

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These are only a few of the many definitions attempted. There were, in fact, so many, that a corrective measure became badly needed. It was supplied by modern American behavioristic psychology, which tended to shy away from erudite inquiry and be content, instead, with operational definition. Thus intelligence, it was decided, was simply "what intelligence tests measure." This may seem circular and arbitrary. But actually it is not, provided that the choice of testing instrument is made according to some clear postulational definition. A test cannot be chosen at random and, *as one writer put it in a discussion of operationism in psychology*, "we cannot measure electricity with a gas meter" (87), so no more can we expect to measure intelligence with a cardiograph. We usually postulate that this trait has something to do with ease of adaptability or solving problems and start from there.

In the present connection, it is important to establish *that the tests* commonly used in psychology can predict certain genetic criteria, such as twin and family resemblances, that is, to establish that the trait they are measuring depends on, or is correlated with, hereditary factors. Obviously, before any inquiry can be made into the gene mechanisms behind intelligence, this primary fact must be demonstrated. This is not a matter for speculation but of empirical check. It can be discovered in the usual experimental way: (*a*) by manipulating heredity and holding environment constant or random; (*b*) by manipulating environment and holding heredity constant or random. These procedures will not, of course, reveal the whole story. Simultaneous variation of both heredity and environment together is needed in order to examine interaction effects. It is quite likely that environment has different effects on different genotypes. However, since no systematic information seems to be available on this point, only their independent effects will be considered.

To avoid possible semantic confusion, it should be stated before proceeding that the terms "intelligence," "basic capacity," "intellectual level" *and other synonyms* will all be used to refer to intelligence as measured by standard tests *under standard conditions*, except when otherwise specified. Testing conditions can be regarded as standard only when the degree of objective difficulty presented by the test items is equal for all subjects. As will be shown later, this reservation is highly important in evaluating the extensive work done on the nature-nurture problem.

THE INHERITANCE OF INTELLIGENCE

In psychology, as in many other of the sciences, it is common to use both human and animal subjects in attacking various problems. Which are chosen usually depends on their suitability to the type of problem. In the study of learning, for example, the rat is often used not because

psychologists interested in learning have a preoccupation with this animal but merely because it is a most convenient kind of subject to use in this kind of work. On the other hand, students of perception usually use human beings because they are capable of communicating with the experimenter and can give verbal reports of their experience which animals cannot. This is entirely reasonable. Unfortunately, however, it has tended to create an artificial division so that an individual may be designated as an animal psychologist or a human psychologist according to the material with which he works, in tacit contradiction to the biological fact that man and animal have much in common. [illegible]

consequently [illegible]
Their separate treatment in this section and the two following is a matter of convenience and in no way implies any hiatus between them.

Human experimentation

With human beings, three sources of data have been used to study the inheritance of intelligence, pedigree records, familial correlational data and twin resemblances. All of these have supplied convincing evidence that a large proportion of the variance in measured intelligence in the population is due to heredity.

The first source, pedigree methods, was first used in a scientific manner by Sir Francis Galton in the latter part of the 19th century. Galton was greatly impressed with eminence which he considered to be so rare as to have an incidence of only 0.025 per cent in the general population. On the basis of reputation and such records as were available, he presented numerous pedigrees of judges, literary men, statesmen, scientists and even university oarsmen (30). All these showed that the chances of an eminent man having an eminent relative were fairly high. To Galton this was apparently clear proof that intelligence was inherited, and he urged against the environmentalist hypothesis that true eminence would not remain hidden but would always surmount social barriers and unfavorable circumstance. In point of fact, the proof was not complete. By its very nature, the pedigree method could not separate nature and nurture. It did not show whether eminent men tended to have eminent offspring because they supplied the latter with good genes or because they supplied them with good environment. This difficulty applies equally to the numerous pedigree studies that have followed Galton's work, such as those on musical ability, mechanical ability, statesmanship and feeble mindedness (cf. Gates 31).

More informative is the second source of data first examined systemati

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It is certainly possible that, with such heterozygous matings as must of necessity be studied, it might be no larger than the usually obtained one of around 0.50. Purely genetic variation alone might well prevent it from being higher, even if environment was maximally homogeneous for all individuals in all families.

The third source of evidence on the inheritance of intelligence comes from twin studies. Twins offer, of course, unusual advantages in the study of inheritance and have consequently been used by a considerable number of investigators. Summaries of the literature have been made by Burks (8), Carter (13), Woodworth (91, 92), Anastasi and Foley (2), Österlingen (59) and many others. In general it is fairly well established that identical twins resemble each other in intelligence more than fraternal twins who probably have an equally homogeneous environment, and considerably more than siblings. Some representative findings are presented in table 13. It is clear from these that the degree of similarity is very marked. In fact, it is about as great, on the average, as the test retest reliability of single

TABLE 13

Intellectual resemblances of identical twins as found by a number of investigators

Investigator	Number of pairs	Correlation
Wingfield and Sandiford (89)	45	90
Stocks and Karn (76)	68	84
Newman, Freeman and Holzinger (58)	50	88

individuals (69). At the same time, it must be recognized that identical twins live in exceptionally similar environments (51) so some caution is necessary in interpreting these results. The clearest supplementary data come from studies of identical twins reared apart. The best known of these, by Newman, Freeman and Holzinger (58), involved 19 twin pairs. The members of some of these pairs were raised in rather similar environments, but the members of others were raised in circumstances which appeared to be very different. The twins Raymond and Richard, for example, were separated at one month of age and reared by the families of a well to do physician and of a truck farmer respectively. The general results give cogent support to the inheritance hypothesis. Although the correlations between the members of the pairs on intelligence tests was found to be somewhat less than is usual with identical twins (Stanford Binet 0.67, Otis 0.73), they were still appreciably greater than those between ordinary siblings reared together. On the other hand, a few pairs differed greatly. It is worth noting that there was found to be a correlation of 0.79 between the amount of educational discrepancy for each twin pair

calls by Karl Pearson in 1903 In a series of articles (61, 62, 63, 64), Pearson showed that the correlation between siblings on mental ratings was approximately 0 50 Since this was about the same degree of magnitude as he had obtained with physical characters, Pearson concluded that psychological functions were inherited to the same degree (61) Similarly he obtained a correlation of about the same order between parents and offspring (0 47) Since Pearson's day, a great deal of information on family resemblances in mental ability as measured by rating scales, scholastic ability and mental tests has been collected Summaries of this extensive literature have been made by Carter (12), Schwesinger (69), Conrad and Jones (17), Sen Gupta (71) Jones (51) Anastasi and Foley (2) and Langfeld (53) among others In general though some investigators have obtained higher (14, 60 84), and some lower correlation coefficients (15 34) Pearson's original figures have been for the most part confirmed There is little doubt that in mental ability children bear a strong resemblance to their parents, and siblings to each other Now as Schwesinger has pointed out (69), the obtained correlations do not necessarily indicate the importance of heredity any more than of environment in determining resemblances Consequently it is necessary to seek supplementary information Fortunately some is available In the first place siblings are much more alike in mental ability than are random unrelated pairs raised in similar circumstances (69) Secondly foster children are usually less like each other and less like their foster parents than true children (7 55) It does appear that adopted children tend to shift towards the intellectual level of the home into which they are placed (26 74) but this may be accounted for at least partially by selective placement (51) Thirdly siblings reared apart out of the home in an institution such as an orphanage (44 54) still maintain a high degree of resemblance Fourthly the correlation between siblings of different ages is not much lower than that between siblings of similar age (16 23 67) even though the environments of different age groups are considerably different Fifthly the degree of resemblance both between parents and children (5) and between siblings (51) appears to increase rather than to decrease with age despite the fact that environment probably becomes less and less homogeneous

All these data point to heredity as an important determiner of intellectual level From the size of the correlations alone however, we can infer very little about the extent of its effect or about the extent of the effect of environment In studies of the kind just discussed many factors can influence the degree of resemblance statistically obtained Homogeneity heterogeneity of the sample method of pairing for purposes of statistical analysis are a few It cannot of course be known how large a correlation might be found in the complete absence of variation due to environment

Animal experimentation

With animal subjects a much greater degree of control is afforded than with human subjects. While on the human level the study of the inheritance of intelligence is essentially the study of natural populations as Gruneberg has pointed out (35), on the animal level it is a matter of exact experimentation. Indeed it is probable that such laws as describe the genetic transmission of intelligence will be found more readily with subhuman material. The great success of formal genetics in this regard suggests that it is not too sanguine a hope that the more basic aspects of psychogenetics may similarly be sought and discovered.

To date animal studies on the inheritance of behavior in general and of intelligence in particular have used two lines of attack, the method of selective breeding and the method of pure strains (cf. Hall, 37).

The first of these involves the selective breeding of strains that are high and low on a certain behavioral continuum. Tryon (85), Heron (43), and Kuppuswamy (59) offer good examples of this technique. The first two of these investigators bred maze-bright and maze-dull rat strains on the basis of error scores on 19 runs in the Minnesota automatic maze, Tryon to the 18th, Heron to the 16th filial generation. Both experimenters showed rather clear differentiation between strains after the 7th generation, beyond which point further breeding did not greatly increase the separation. Similarly Kuppuswamy selectively bred 10 generations of rats on the basis of performance on a water maze, also obtaining a separation between high and low scorers.

Now these experiments have been useful. But they have suffered from two main defects. In the first place it is very doubtful if in any of them postulated rat intelligence was really being measured. Both Tryon and Heron expressed doubts regarding this and some time later Searle (70) showed definitely that Tryon's brights and dulls differed markedly in many other traits besides intelligence, such as activity, emotionality, and performance in a water maze. From the scores made by animals on thirty measures in nine different

of personality prof

geneous within ea ... groups but were quite dissimilar between groups. His general concl...

... on maze

... in terms of motivational and emotional patterns. Thus the two strains could hardly be called intelligent and unintelligent. The ability for which they had been bred appeared to be specific to the particular type of maze used and it was probably not purely

and the difference between them in Binet *IQ*, (0.53 for Otis *IQ*). Thus environment was certainly not without some effect though this was probably overemphasized by Newman et al. (58). Several other less extensive studies of twins reared apart by Muller (57), Saudek (68) and Burks (10) are in essential agreement with the conclusion that their intellectual similarity is not greatly lowered by environmental differences.

In summary of the evidence obtained from experimentation on human beings it may be stated that heredity is an important determiner of intellectual level. It is probably futile however to try to inquire into the extent of this determination, as Anastasi and Foley (1) and Hebb (41) have pointed out. The nature of the interaction of nature and nurture is highly complex and it is probably a misrepresentation of the case to attribute, as Burks (9) and Cattell (14) have done, so much of intellectual ability to heredity and so much to environment.

Now the general conclusion that intelligence is inherited does not necessarily imply that an intelligence test always reflects inherited differences. It will only do so in the case that it presents an equal degree of objective difficulty to the individuals being compared. This condition is generally fulfilled within certain homogeneous segments of the population. But it is often not fulfilled between these segments and for two main possible reasons. In the first place there are some grounds for suspecting that many tests such as the Stanford Binet are biased against many individuals in the population predominantly of the lower socio-economic class (33). The Binet was in fact standardized on middle class subjects and consequently the language in which many of its problems are couched is often quite unsuitable for children at lower social levels. A child may thus fail an analogy when it involves terms outside his experience but may solve it easily when more familiar words are substituted without changing the actual form of the problem. This puts a definite limitation on the use of intelligence tests in the study of heredity. It is highly desirable that all levels of society be studied but only on condition that the test used is standard throughout the population.

Now this is really a psychometric problem (51). A second possible reason why intelligence tests may reflect non hereditary differences is that environment may have potent effects on intellectual level and that these effects may vary systematically in different sections of the population. This is more than merely a psychometric problem and a definitive solution to it is of great importance both to scientists and educators. Consequently it will be considered at some length in the ensuing section. First however the animal evidence bearing on the inheritance of intelligence will be discussed.

it is not used Second by the use of many short problems, a fairly wide range of an animal's ability is sampled In these respects the Hebb-Williams maze is somewhat homologous (as intended) to a human intelligence test (49) The latter is only taken by subjects who have had certain preparation, i e, schooling etc and it involves a large variety of short items

To date six generations have been bred and tested Mean scores of bright and dull animals of each generation are presented graphically in figure 44 It is clear that a marked separation between the two strains has

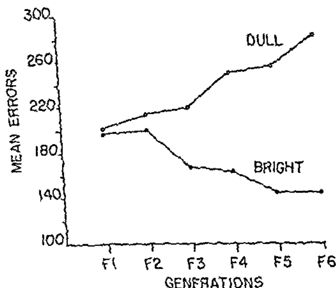


Fig 44 Mean error scores of bright and dull rats selectively bred on the Hebb-Williams maze over six filial generations

already been established In fact as early as the F_3 a significant difference appeared between them and in the following F_4 generation only two cases of overlap between brights and dulls appeared

Although as stated already, the maze procedure used tended to eliminate the possible contribution of traits other than intelligence to the score of an animal it was considered possible that the two strains might still show irrelevant differences prior to testing A number of simple tests was given to examine this possibility (79) In general no differences were found between bright and dull rats either in weight or emotionality Brights tended to be somewhat more strongly motivated by food, but this difference was not significant In a simple elevated maze, the two strains showed an approximately equal amount of exploratory behavior

intelligence as intended. This criticism applies equally to the studies of Heron and Kuppaswamy.

A second difficulty, important to the study of the genetic mechanism underlying intelligence, lies in the fact that none of the investigators mentioned used inbreeding to any degree. The resulting lack of homozygosity in their strains naturally precluded any possibility of making a genetic analysis. Thus when Tryon made crosses between his two strains he obtained an F_1 with as large a variance as the F_2. This ended further work on the problem.

In view of these deficiencies, all the selective breeding experiments, while valuable in a general sense in that they support conclusions gained at the human level, *have not contributed much additional information on* the inheritance of intelligence. They indicate beyond question that certain complex types of behavior are inherited, but they do not show how they *are transmitted. Consequently, further experimentation has been needed.* In an attempt to fulfill this need, a program of research has been initiated at McGill University.[*] This will now be described.

The experiment was designed to meet those two requirements which have not been met by previous studies, namely (*a*) that selection be made on the basis of operationally defined rat intelligence *and that trait alone unconfounded with other unknown traits; (b) that a high degree of homozygosity* be achieved in each of the two lines by means of inbreeding.

The Hebb-Williams maze was considered to be highly suitable to meeting *the first requirement. This maze consists of a square enclosure with* movable wire mesh top, a starting box in one corner, and a food box diagonally opposite. Barriers of varying length placed in a number of different *positions between the starting box and the goal constitute the problems.* Twenty-four such problems have been designed, the second twelve being reverse mirror images of the first twelve. Procedure is as follows: the animals are put on *a twenty-three hour food deprivation schedule* and trained in the maze on a preliminary set of six practice problems until they are thoroughly accustomed to the situation and run directly to food *within a certain time limit. Following this,* the set of twenty-four test problems is given to each rat, one problem per day. Scoring is in terms of errors (entry into a *cul*), and time from start to food. Two main advan*tages are afforded by this method. In the first place, the pretest training* tends to eliminate motivational and emotional differences between animals. Unless a rat becomes completely adapted to the maze and to handling

[*] This program was conceived by [illegible] at the University of Illinois. It was continued by the author from the F_3 to the F_6. Both the selective breeding and the experiments reported here were supported by grants-in-aid from the National Research Council of Canada and the Rockefeller Foundation.

So far, only a preliminary attempt has been made with the mouse strains to study a trait as complex as intelligence The Hebb Williams maze procedure was found to be fairly serviceable, though some modification of it will probably be necessary before it is really practicable At least at first it is perhaps advisable to confine work to as simple behavioral traits as possible in order to establish a firm foundation for subsequent study

In general both the method of selective breeding and the use of inbred strains confirm the conclusion gained from human experimentation that hereditary factors are highly important in determining intellectual ability To gain more information, however, many more studies will have to be made both with animal and human material Problems that occur in natural human populations can readily be duplicated in the laboratory for

TABLE 14

The inheritance of activity Mean parental and F_1 scores in 3 different inbred mouse strains

	Strain	100 × Log Score	
		Test 1	Test 3
Parents	BR/a	271	215
	AKR	212	239
	BALB/c	73	199
	A/Jax	48	146
F_1s	BR/a × BALB/c	257	231
	BR/a × A/Jax	237	219
	AKR × A/Jax	[illegible]	[illegible]

more exact observation Theories formulated to describe the genetics of human intelligence can well be tested on animals Indeed, it is likely that such a coordinate program will be necessary before any really basic data in psychogenetics can be obtained

The next question to be examined is the extent to which intellectual capacity can be altered [illegible] discussed there [illegible] have a marked c[illegible] it, and that when it does this may be due to bias in the testing instrument rather than a real change in basic capacity of the subjects Evidence bearing on the problem will now be discussed

ENVIRONMENTAL EFFECTS ON INTELLIGENCE

As we have already pointed out it is probably not legitimate to attribute a certain proportion of intelligence to heredity and the remainder to environmental factors A given degree of intelligence is produced by both working together Neither is anything without the other Nevertheless, it

(78) but in an enclosed maze, dulls tended to explore rather more than brights (82) On the whole, however, there are some grounds for supposing that the two strains differ mainly in intelligence as measured Other tests of maze ability have yet to be tried

The second requirement of homozygosity mentioned above has not yet been satisfactorily met due to the infertility of many of the brother sister matings particularly in the last generation (F_6) In fact in order to insure survival of the strains random matings were necessary However when numbers have been sufficiently built up again inbreeding will be resumed

In summary the two lines being selected should eventually provide useful material not only for a thorough genetic analysis of intelligence but also for the analysis of the psychological and physiological bases of brightness and dullness Indeed a solution to the second problem should greatly aid a solution to the first

The second method in animal experimentation on the inheritance of intelligence involves the use of material known to be genetically homogeneous *Ideal subjects* in this connection are the eighty odd homozygous mouse strains bred by twenty or more brother sister matings Procedure with inbred strains involves simply the discovery of strains which are *widely separated on some behavioral parameter followed by suitable* crosses and genetic analysis Bagg (3) with a multiple choice box and Vicari (86) with a simple maze made promising attempts with several strains But *although both demonstrated strain differences* they were not able to make satisfactory genetic analyses From a purely genetic standpoint the best work in the area has been done by Hall (36) and Fuller et al (27 28) on audiogenic seizures From a psychological standpoint however this experimentation is of less significance More work on *normal* behavioral characters is needed

Conjointly with the McGill selective breeding program outlined above an attempt is presently being made by the author to test samples from as many mouse strains as possible on a number of fundamental behavioral measures So far fifteen strains have been tested on measures of food drive activity and emotionality Although intrastrain variability was found to be marked striking differences between some of the strains appeared Since the second of these traits activity is the easiest to measure reliably more intensive study is now being devoted to it F_1s between *some of the* strains most widely separated in activity have already been tested on two measures and F_2s and backcrosses have been bred and will be tested shortly Some *results are presented in table 14 It will be noted* that the sizes of the F_1 means in relation to the two parental means are rather different in the two measures of activity This genetic fact suggests that the tests involve somewhat different types of behavior It is hoped that the picture will become clearer when more crosses have been tested

(83) and Burt (11) have stated Even in those cases in which changes have occurred it is probable that the changes were due, not to an increase or decrease in basic capacity, but rather to an increase or decrease in educational equipment necessary to understand the problems in the test This may of course be regarded as a change in intellectual performance, but it is probably incorrect to call it a change in basic capacity, since testing was not carried out under standard conditions

Animal experimentation

Results obtained from animal work however, are far more definite With rats which are normally reared in the rather homogeneous environment of a laboratory cage an enriched living space in early life with a greater range of perceptual stimulation clearly improves learning ability in

TABLE 15

A comparison of hereditary and environmental effects on the intelligence of rats

	Error Score on Hebb-Williams Maze
Hereditary dull	2[illegible]9 5
Environmental restriction	234 5*
Hereditary bright	14[illegible] 8
Environmental free	137 3*

* Scores based on data of Forgays and Forgays (25) and Hymovitch (50)

adult life (6 25 39 50 90) In fact as shown in table 15 the amount of variance that can be produced in rat intelligence by altering environment is almost as much as can be obtained by selective breeding for brightness and dullness

Similarly with dogs Thompson and Heron (80 81) have found that restriction during the first 8 10 months of life causes a marked deficit in problem solving ability and a general retardation in psychological development characterized by hyperactivity and puppy like behavior Further these changes appear to be fairly permanent showing up in dogs out of restriction for two or three years

Thus there does seem to be some discrepancy between the human and animal data The reasons for it however are fairly clear In the first place, the variations in environment made with animals have been much more radical than is possible with human beings While an orphanage may be relatively unstimulating it probably provides the basic essentials for the maturation of the intellect It offers about as much experience as a home does and perhaps even as many every-day problems to be solved On the other hand the nursery school while increasing the social and emotional

is still possible to study them independently by varying one and keeping the other as constant as possible or randomizing its effects. The present section will deal with the amount of variance in intelligence that can be produced by different kinds of environment. As before, both human and animal experimentation on the problem will be considered.

Human experimentation

With human beings, a large number of studies have been made dealing with the effects both of an enriched and an impoverished environment on intelligence. On the side of enrichment, much time and effort has been devoted to studying the effects of nursery school attendance on *IQ*. On the whole, the results have been inconclusive. A number of studies have claimed positive results (88), but an equally large number have failed to demonstrate any effects (51). Since even one clear cut negative experiment can cast doubt on conclusions based on many positive ones, the problem must remain unanswered for the time being.

On the side of restriction, the evidence is also ambiguous. Cross-cultural observations of children raised in rather confining circumstances, such as the studies of Dennis on the Hopi (21) and Danzinger and Frankl on Albanian children (18), have failed to show marked effects later in life. There have been several case studies of individual children reared in extreme isolation, such as those of Davis (19, 20), Mason (56) and others, but these are unfortunately very difficult to evaluate, since many other factors besides restriction, such as the intelligence level of the parents and the health of the child, were also operating. Perhaps the most well known studies claiming positive results have been those on institutionalized children. Skeels and Dye (72), for example, found a mean loss of approximately 26 *IQ* points in a group of 12 children after two and a half years in an orphanage. This rather startling loss was contrasted by the authors with an even more striking gain of about 28 *IQ* points made by a comparable group reared by moron nursemaids in an institution for feeble minded children. The net difference between the groups of 54 *IQ* points represented the effects of an unstimulating environment. However, since Skeels, Updegraff, Wellman and Williams (73) found that the loss for another group in the same orphanage was only about 5 *IQ* points, the first result must be regarded as rather suspect, as Goodenough, Terman and others have pointed out (32).

We may add to the above a number of studies dealing with rural-urban and racio-cultural comparisons (cf. Jones, 51), some of which have favored the environmentalist hypothesis, but on the whole the main body of evidence does not convincingly demonstrate that environment can markedly change measured intelligence, as Goodenough (33), Jones (51), Thomson

done by Fisher (24), Hogben (45, 46, 47) Wright (93), and others (4 66 75) relating correlational analysis to Mendelian genetics, but it has not so far been exploited empirically by scientists interested in the field There is a pressing need for a fusion of the two lines of research

So far only two attempts have been made to construct a theory of the genetics of intellect The first of these was made by Hurst (48 49) He based it on two sets of data, (*a*) the Woods Royal Family data, consisting of intelligence ratings of 212 Royal families of Europe, with 424 parents and 558 offspring (*b*) his own Leicestershire data consisting of *IQ* scores of 194 families with 388 parents and 812 offspring Examination of these data indicated two distinct family types a segregating and a non segregating that is a heterogeneous and a homogeneous type To explain this Hurst postulated one major gene pair, *Nn* and five minor modifiers, *Aa*, *Bb Cc Dd Ee* Any individual having *NN* or *Nn* was normal—grade 5 in Hurst s scale of intelligence (*IQ* 90–110) That is to say, *N* was a dominant gene for average intelligence and in its presence the minor genes would have no phenotypic effect In the absence of *N* however, the minors *A*, *B*, *C D E* would act as unit increasers and the minors *a*, *b*, *c*, *d e* as unit decreasers Thus the non segregating families having an incidence of one third in the population would have both parents homozygous for *N*, or one homozygous and the other heterozygous producing all mediocre children—all with *N* The segregating families however, having an incidence of two thirds in the population would have both parents homozygous for *n* or one or both heterozygous and would produce any grade of offspring depending on the minor modifiers when *N* was absent Hurst found that this genetic formulation described his data rather well However as Conrad and Jones have pointed out (17) the theory lacks an independent test An analysis of the *F* or third generation though rather impracticable would have been desirable as would also a correlational analysis with an application of Fisher s formulae As it stands the theory is a worthy attempt but cannot be regarded as completely adequate It does deserve perhaps to be tested on other data both human and animal

A second theory of the genetics of intelligence has been proposed recently by Pickford (65) This formulation rests on a simple blending hypothesis Pickford [illegible]

[illegible] a simple blending theory [illegible]

retic [illegible]

usua [illegible]

work [illegible]

corr [illegible] empirical

[illegible] its to fit the blending hypothesis so the latter cannot

development of a child (51) does not add very much more than the home in the variety and amount of perceptual and intellectual stimulation it affords. With animals, however, there is a vast difference between the restricted and free environments which can be imposed. Such extreme conditions are of course not feasible with children. Secondly, it is likely that for human beings the period of restricted or enriched environment neither starts soon enough nor continues long enough to produce marked effects. It has been customary to place animals, however, in the experimental environment from the time of weaning or earlier and continue this till maturity. For humans a corresponding period would be from about 9 months to 14 years of age. Consequently, in view of these two differences there are reasonable grounds for the discrepancy between human and animal experimentation on the subject.

In summary of the foregoing section, it may be concluded that environment can have a very marked effect on basic intelligence with two reservations. First, to alter it, environment must be very different from normal. If it fails to supply certain minimum requirements in the way of sensory and perceptual experience, it is probable that an intellectual deficiency will result. However, there is no real evidence to show that an environment supplying much more than the minimum requirements will benefit intelligence. This is not to say, of course, that ability to do specific intelligence tests may not be changed. The twins Gladys and Helen of the study by Newman *et al.*, for example, showed a difference of 24 IQ points. But this was probably due to the fact that there was a great difference between them in the amount of formal education received, with the result that the tests given to them did not offer the same objective degree of difficulty in both cases. It is easy to see that a complete lack of training in arithmetic would be a great handicap in taking most intelligence tests. But the low score consequent on this lack would not necessarily mean lower basic intelligence. The second reservation is that it is probably only in early life, prior to maturity, that environment can have any marked effects. Both Wolf (90) and Hymovitch (50) have shown with rats that restriction (or enrichment) later on in life does not cause appreciable changes. Evidence from the study of brain damage, as Hebb has indicated (40), also points to this conclusion. An injury early in life has much more lasting and widespread effects than a similar injury later on. In a sense, early environmental deprivation is an analogous case, since it hinders function and consequently normal development.

THE GENETICS OF INTELLIGENCE

At present very little information is available on the genetic mechanism transmitting intelligence. Some excellent theoretical work has been

Secondly, it may be stated with some assurance that environment can exert fairly permanent effects on basic capacity under certain conditions. Animal studies show that severely restricted environment early in life can result in a marked deficiency in intellectual ability later on. While this negative effect is clear, it is doubtful that adding to the stimulation value of environment beyond a certain minimal level will do much to increase intelligence.

With regard to the genetics of intelligence, almost nothing is known. Two theories concerning it have been formulated, but since they do not explain certain known facts, such as regression and variability of siblings at different levels of parental *IQ*, they cannot be considered adequate. This is rather a negative conclusion. On the positive side, it may be said that at least some of the basic requirements for any potential theory are known, although even these may be subject to revision when further information is brought to light.

When balanced against the large amount of work that has been done in the area, these conclusions may appear rather meager. Clearly, much remains to be done. Before closing, we may suggest a few possibilities.

In the first place, with human beings, tests other than the standard intelligence tests should be tried. Measures which are thought to reflect the integrity of the brain, such as those of Halstead (38) and Teuber and Bender (77), because they are closer to structure, might well provide useful information on the inheritance of intelligence. Or again, relatively pure tests of special abilities, such as those derived by the techniques of factor analysis could be used. It is likely that twin or family resemblances might prove greater or smaller on different intellectual factors. Although they will not be *enumerated here*, there are many other possibilities besides these. It should be emphasized that the tests used in the past may not have supplied a complete picture and may even have supplied an inaccurate one.

Secondly, there is a need not only for independent human and animal researches but also for coordinated programs. As stated previously, many of the problems occurring in natural human populations can easily be duplicated with animals in the laboratory. Any degree of kinship can be bred and the resulting data analyzed mathematically for comparison with analogous cases at the human level. This should prove exceedingly valuable in achieving an understanding of the genetic mechanisms behind the transmission of intelligence.

Thirdly, more physiological and neuro a ate [illegible]

[illegible] their significance in controlling

be necessarily dismissed on these grounds alone Conrad and Jones also suggest another deficiency of blending theories, namely their inability to account satisfactorily for regression of offspring to the population mean Regression up to a certain point can be explained statistically Beyond this point, a genetic explanation may be necessary This cannot be afforded by a simple blending theory

Obviously the matter is highly complex and much work remains to be done before any adequate formulation can be made However the minimum requirement of any theory is that it account for several basic facts Some of these have been reviewed by Conrad and Jones (17)

In the first place, intelligence is a quantitative character with a rather wide dispersion This implies multiple genes though not necessarily equal and additive ones Secondly there is some indication that offspring regress below or above mid parental level toward the population mean (14 49 60) Although this may be partly explained by a statistical or an environmental hypothesis genetically it implies recessivity of extremes and dominance of normality Thirdly, variability of sibling intelligence appears to be greatest at the middle ranges of intelligence, smaller towards the extreme (17, 60) This tendency is not marked but it is definitely not the other way around as would be implied by dominance of average intelligence Fourthly parent child correlations in intelligence have been found by many workers (14 17, 60 61) to be equal to or greater than sibling correlations According to a theory of dominance the sibling should exceed the parental correlation However, as Conrad and Jones have pointed out (17), even with complete dominance, the correlations may be equalized by the influence of homogamy

These then are some of the basic data which any theory of the genetics of intelligence must explain It is possible of course at least in the case of the second two points that they may be contradicted by further experimentation It may be that the present amount of information available is insufficient to make any serious formulations and that only when more has been obtained will a solution to the problem be more feasible

CONCLUDING REMARKS

From the above discussion it is clear that several general conclusions regarding the inheritance of intelligence have been fairly well established

First, data gained from pedigrees, familial correlational data twin studies, and animal experimentation indicate beyond a doubt that intelligence is inherited so that in most cases the intelligence test score does represent basic inherited capacity This may not be true in all cases however, particularly in the lower ranges, due to bias in the testing instruments used

Secondly, it may be stated with some assurance that environment can exert fairly permanent effects on basic capacity under certain conditions Animal studies show that severely restricted environment early in life can result in a marked deficiency in intellectual ability later on While this negative effect is clear, it is doubtful that adding to the stimulation-value of environment beyond a certain minimal level will do much to increase intelligence

With regard to the genetics of intelligence, almost nothing is known Two theories concerning it have been formulated, but since they do not explain certain known facts, such as regression and variability of siblings at different levels of parental *IQ*, they cannot be considered adequate This is rather a negative conclusion On the positive side, it may be said that at least some of the basic requirements for any potential theory are known although even these may be subject to revision when further information is brought to light

When balanced against the large amount of work that has been done in the area these conclusions may appear rather meager Clearly, much remains to be done Before closing we may suggest a few possibilities

In the first place, with human beings, tests other than the standard intelligence tests should be tried Measures which are thought to reflect the integrity of the brain such as those of Halstead (38) and Teuber and Bender (77) because they are closer to structure, might well provide useful information on the inheritance of intelligence Or again relatively pure tests of special abilities such as those derived by the techniques of factor analysis could be used It is likely that twin or family resemblances might prove greater or smaller on different intellectual factors Although they will not be enumerated here, there are many other possibilities besides these It should be emphasized that the tests used in the past may not have supplied a complete picture and may even have supplied an inaccurate one

Secondly there is a need not only for independent human and animal researches but also for coordinated *programs* As stated previously, many of the problems occurring in natural human populations can easily be duplicated with animals in the laboratory Any degree of kinship can be bred and the resulting data analyzed mathematically for comparison with analogous cases at the human level This should prove exceedingly valuable in achieving an understanding of the genetic mechanisms behind the transmission of intelligence

Thirdly more physiological and neuro-anat

behavioral differences is unknown, except in the case of a few gross defects Such known variations as those in the autonomic and endocrine systems, in biochemistry, protein synthesis and general physiological reaction of the nervous system deserve to be explored thoroughly This should aid not only our understanding of the inheritance of behavior, but also our understanding of the basic principles of behavior

DISCUSSION

DR J P SCOTT [Bar Harbor, Maine] I have followed these experiments of Dr Thompson with a great deal of interest because they run parallel to a research program which we are doing at the Jackson Laboratory on the effects of heredity on the social behavior and learning abilities of dogs

The literature in the field indicates that selection can produce strains of animals which will learn particular things better than others By selecting in opposite directions Tryon produced one strain of rats which would learn a maze readily and another which learned it poorly In dogs the selection has been carried out by dog owners over a period of centuries and there is no doubt that Beagles are easy to teach to hunt rabbits and that Sheepdogs are easy to teach to herd sheep The existence of this kind of differences can be taken as established

The thing that cannot be taken for granted is what causes these differences Are they the result of differences in intelligence? With Tryon s rats later experiments showed that Tryon had not selected for dullness or brightness as such but rats that responded emotionally to the maze and those which did not Any experiment which is done with learning or so-called intelligence must be done in such a way that emotional responses are measured

Dr Thompson has explained how he tried to eliminate these factors in his experiment but it has occurred to me and I would like to have him comment on this that in the Hebb Williams maze a rat which had a stronger tendency to explore the environment might have a considerable advantage over another In other words is there a possibility that the rats are being selected for a strong or weak exploratory drive?

One other point which I would like to emphasize is the fact that all the evidence so far indicates that genetic differences in learning ability are very specific in nature We have given a large variety of tests to our dogs and find invariably the more specific the test the greater the likelihood of obtaining differences between strains Measures of overall adjustment as in the total scores of tests (which incidentally is the type of measure used in many human intelligence tests) usually bring out comparatively small differences between strains

When the special parts of a test are analyzed we often get clearcut differences which seem to have a genetic basis This is related to a point which was made yesterday, namely that primary gene action affects some biochemical or physiological process The more closely behavior can be related to some simple physiological process which means the simpler the behavior the greater the likelihood of discovering clearcut genetic differences

DR ROLAND P MACKAY [Chicago Illinois] I should not like to involve Dr Thompson in any semantic difficulty but when he says that environmental restriction seems to reduce the intelligence of the animal as much as any inbred defect I wonder whether such a statement does not need clarification

It would appear that the performance of the animal is reduced by environmental restric

would a more felicitous environment will depend upon the emotional structure of the individual

Dr K S Lashley (Orange Park, Florida) Dr Scott said yesterday that heritable differences in behavior must be an index of structural differences I think we have one key to the solution of this structural problem, the microscopic variations in the central nervous system In comparing the brains of a few monkeys we have found enormous individual differences in limited areas of the cerebral cortex Cell size or cell concentration may differ by as much as 50 or even 100 per cent in corresponding gyri and there are even great differences in the cell types occurring in corresponding areas Equally great differences in cell sizes and types are apparent when thalamic nuclei are compared and even the gross structural arrangement of the nuclei may vary

No comparable studies of histological variations in human brains have been made, but the lack of agreement in description of

[illegible] potential each among monkeys

The task of analyzing variations in microscopic structure and correlating them with behavior differences is a gigantic one but eventually it must be carried out, if we are to understand the genetic structural basis of individual capacities

Dr W R Thompson (Closing) First of all in reply to Dr [illegible]
evidence that the bright and dull ra[illegible]
behavior I don t think however tha[illegible]
maze ability

The way I have [illegible]
maze which the rat tr[illegible]
only by exploration itse[illegible]
than for the dulls Th[illegible]
other words *learning* [illegible]

[illegible] result is the same [illegible] level In both cases, however,

I have no data to offer on the second point [illegible]

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one body of valid knowledge which, as a main thread running through the fabric of human personality development, from conception through pregnancy, birth and the epochs of infancy, childhood and adolescence into adulthood, satisfactorily connects genesis with end result. There are many important observations on fetal and infant behavior, particularly neurophysiological and psychomorphological, but these have not been shown to relate directly to the development of emotions, character or personality. In some of these studies the embryogenesis of the brain and postural behavior have been used as prototypes to explain the development of social behavior in later life. The logic of such assumptions is not clear. Some investigations dealing with spontaneously developing patterns of behavior have considered them as if they occurred in a vacuum without benefit of environmental and cultural influences. There are many so-called normative descriptions of behavior at various age levels of infancy and childhood. Frequently these amount to an enumeration of behavior characteristics with grouping into normative or typical configurations. Observations which seemed to follow one another in sequence, with statistical regularity, are assumed to be functions of chronological age. Another deficiency in studies of normative behavior is that they have not been concerned with developmental variations within the range of so-called normalcy, nor with implications of such variations on personality formation. Another defect is that they do not explain the *meaning* of behavior, nor how a relationship of one stage of personality development with another, nor even of one behavioral trait or constellation of traits with others. These formulations of normative behavior have frequently led to anxiety and apprehension in parents who have taken the correlation of behavior and chronological age as absolute, expecting every child of X years to behave like every other child of X age. These parents, like the psychologists promulgating this concept of development as a basis for child rearing, have not appreciated the fact that even at the same chronological age period of X years there may be up to a twelve month difference in age between the child who has just reached his X birthday and that one who is approaching his Y birthday. It is also forgotten that there are psychological as well as biologic differences between children of the same age but who are of the opposite sex, such differences being particularly striking in the pre-pubertal girl in comparison to the boy of same age. Most normative studies are also characterized by their complete avoidance of consideration of the influence of unconscious mechanisms. As one investigator put it:

We wish to avoid the suggestion that the personality of the infant and child is a product of emotions which operate in some mysterious way through the subconscious or otherwise.

It is reasonable to assume that the human infant is born with heredit ary

CHAPTER XIV

RESEARCH ON PERSONALITY DEVELOPMENT OF THE CHILD

MILTON J. E. SENN[1]

Since results of research on personality development of the child like any other research depend so much on the adequacy of methods, it is in order to evaluate methodological approaches frequently used in such studies.

The term personality is defined variously by laymen and scientists alike. For the purpose of this paper, personality means the ability to feel, learn, think and react as a human being who more or less is able to appreciate himself as an individual separate from other human beings and from impersonal objects. This definition implies that personality includes processes of interaction within the person as well as some which go out from him as he relates to others. Personality includes behavior but it is much more than behavior. It embraces intellectual, emotional and social functioning. It is recognized that these functions are dynamic and change from time to time and from one situation to another. It is believed that each personality has a beginning, a development, and that it changes throughout life. The assumption may be made that personality development has continuity, that it begins even before birth, and proceeds in more or less regular fashion to a point of final maturation which is particularly distinct for each person. It is also assumed that each individual progresses at his own rate and rhythm, determined by such factors as physical, psychological, social and cultural forces. Throughout the course of personality development there seem to be nodal points or periods of crisis which the individual must master. His responses at these times are in part conditioned by what he has experienced before, but also by the equipment that he brings with him and is able to utilize at any one time. As he grows the human being acquires some conception of himself and in his relationship with others behaves in a way that is individual to him.

At the present time there are many theories of personality development but these are without consistency and admittedly are inadequate. On the other hand, there is an accumulating body of factual knowledge about behavior. These data come from many sources but as yet do not add up to

[1] Yale University School of Medicine.

Another important requirement, according to my thinking, for research in the future is that studies be long term as well as integrated Such investigations should be started as early in the life of the organism as possible, and extend forward into time for many years with the focus being on the same individual or the same groups of individuals Cross sectional studies should be made to verify or complement hypotheses stemming from the longitudinal approach The multiplicity of data collectable by any multidisciplinary and longitudinal appraisal makes it necessary for the investigators to set a limit on the areas as well as the foci of particular interest It is obvious then that there need to be many different studies of long term duration which are similar only in their general methodology As examples of two such research projects which have similarity, but yet are unique there may be cited the work of Benjamin and Washburn at the University of Colorado a team particularly interested in the psychology of pregnancy as it influences infant care and child development, and that of Kris Mohr and Wolf at the Yale Child Study Center with which I am closely identified

The Yale study was begun in 1949 when a group of married couples was selected from the University prenatal clinic because they were facing the first preg

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... th and mental health During the pregnancy there were several recorded interviews with either a psychologist or a psychiatric social worker with attempts being made to learn as much about the informants as possible particularly their own life situations experiences feelings and attitudes toward pregnancy and matters of health, and particularly child rearing Just before term another member of the research team was introduced to each pregnant woman This was the research pediatrician who would be present at the time of delivery, observe the labor and the delivery (which was without anesthetic) and record not only the observations on the physical aspects but also note verbal expressions as well as attitudes of the woman in the process of giving birth to a baby and receiving it into her own arms Coll ... data dealing with ...

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... investigation was the appraisal of neonatal equipment how this differs from one individual to another and how it serves the purpose of the newborn The team of psychologists social workers and pediatricians were joined by other psychologists particularly trained in observing the infant by the method of K Wolf (3) Examinations

functional patterns which are innate to its structure and are part of its phylogenetic inheritance But the direct relationship of genic inheritance in the development of emotional and personality traits must yet be proved Then too the fact that each neonate arrives into the world with his own constitution and that this influences his later life development is accepted by every one but the fact that there is yet no conclusive evidence to support the theory that a specific relationship exists between personality and body type warrants reminding at this time

Scientific evidence to explain the genesis and development of the human personality has also not been provided by clinical investigations One finds interesting descriptions of behavior and theoretical formulations of its meaning, but without proven demonstration of the relationship of most infantile experiences and later life emotional status behavior and personality An exception may be cited in the demonstration of a long term and possible lasting influence of maternal separation in infancy as reported by Freud and Burlingham (1) and reviewed by Bowlby (2) Psychoanalytic propositions although stimulating for further research in therapy as well as in the field of personality development, in general have been gained by a reconstructive approach They are frequently not specific enough to explain the interacting experiences which characterize child development Here again one sees parents made anxious in child rearing when guided by persons who are either misinformed about psychoanalytic theory or who make unsound applications of it

After this rapid appraisal of what is known or rather what is not known about personality development it may be in order to ask why there exist such large gaps in our knowledge particularly the lack of demonstrable relationship between one set of developmental facts with others whether the research be clinical or experimental It seems to me that so little is known because of a lack of continuity as well as a narrowness in the methodological approaches to the study of human development so many of the investigations have been fragmentary carried out by persons isolated by their own points of view or prevented by physical obstructions from working with others Methods of research must continue to represent the individuality of the investigator and cannot be devised for him or apart from subject matter and material available for his research But as a generality it may be stated that no longer can workers interested in human personality development operate alone in a single field whether this be natural biologic or social science, or psychoanalysis Inter disciplinary research is difficult to initiate and even more difficult to carry out because its members tend to prefer working as individuals instead of in an integrated team There is always danger of a splintering off as one group or a single member of a discipline is motivated to follow a lead which is particularly challenging

organ system as opposed to others and there is variability with which each neonate uses his equipment in mastering such important life situations as accumulation and discharge of tension

Whether this variability of response continues with maturation and whether it changes into even more specific differentiation of part functions needs to be demonstrated If differentiation follows developmentally, it is important to try to distinguish which forces in time and space are the most important determinants of change as well as what body systems are in interaction with each other

From observations of the growing infants in this study, it is clear that the neonatal pattern of wholeness—functioning with some specificity of response in tension reduction is modifiable through the development of awareness of human and non human objects in the environment Of these, the human elements which in the first few weeks of life seem indistinguishable from the non human because of the inadequacy of the newborn equipment and because of the symbiotic relationship of infant with the mother become increasingly effective in providing opportunities which non human objects cannot provide For example a mother who provides pleasure by giving food or who frustrates by withholding sets up paradigms of reaction which can become models for such mental mechanisms as imitation and identification Later in infancy at a different age for each subject observed we have watched how the stress of toilet training is coped with This permits a developmental approach to the study of the mechanism of sublimation and its use as a defense and provides another base with which to compare later life behavior The mother as a distinct person bringing with her cultural values prevalent at the time and her own ethnic tradition remains the central human figure for many months and it is not until about eighteen months or so that the father and other family members appear to be distinguished from the mother and become effective in influencing the differentiation of the infant The use of non human objects as stimuli in the environment with which to relate in a tension creation and reduction maneuver begins as early as the third month when the development of the eyes has proceeded to a point where they may see objects The eye may be said to take in stimuli which result in tension accumulation or again contrariwise as tension reducers At about this age the hand also is used not only to grasp and bring objects to the eye and to the mouth but as an instrument to discharge tension in a variety of physical movements

The advantages of a long term study should permit one to observe whether methods of meeting stress in infancy and childhood are carried forward into later life to become bases for deviant behavior, character

regularly in a well baby clinic at the Child Study Center, as well as in the home, provided data on each infant as he grew and changed physically and behaviorally. Facts about the parents as persons, as well as information about the total environment and specific environmental influences which seemed experientially important were recorded. For example, the influence of a physical illness in the parent or in the child himself was noted. The changes in methods of child care were particularly observed. The manner in which parents and child and infant met crises were of special interest. For example, how the mother-infant couple handled changes of feeding behavior, or how changes in physical development brought out new forms of motoric discharge in turn evoked emotion in all members of the family. When each infant studied reached the age of two years, placement in a nursery school was considered, and if it seemed unprejudicial to his health or development he was gradually introduced to this new experience. Here again he was observed both as a member of a group and in individual play sessions.

Early in the investigation the hypothesis was formulated that every developmental step entails an individual solution; that there are different ways by which developmental progress may be made successfully. The aim of our study, then, was that of appraising the variability of children's behavior. A second hypothesis to be tested stated that a child's individual solution of any developmental step is a result of a continuous interaction of his specific equipment and his environment. Individualization was conceived of as an infant's personal way of solving problems, or in terms of a modern way of psychiatric thinking, how he meets and copes with danger and with other stressful situations. From observations of the newborn it seems that the earliest observable indicator of meeting stress is a disturbance of his equilibrium with rising of tension. The earliest behavioral manifestations of problem solving, therefore, lie in his modes of tension management. In the project described, each newborn was studied in terms of his individualization by observing the specific tension creation and tension reduction situations which came into his life and how he handled them. From a preliminary analysis of the observations during early infancy it appears that the most important mechanisms dealing with tension are found in the gastro-intestinal tract, particularly the mouth; the sensory system, especially the skin; the motor discharge system; and sleep. Crying, sucking, biting, grimacing, breathing heavily, and kicking all serve to help reduce tension. Rubbing of the skin and physical restraint also serve this purpose. Although the newborn reacts to both internal and external stress with a wholeness of himself and with generalized patterns, already at that early age he seems to show a greater excitivity and reactivity in one

CHAPTER XX

GENETICS OF THE LIPIDOSES

C. NASH HERNDON[1]

Since the time when Garrod (15) popularized the phrase "inborn errors of metabolism" to describe the group of primary metabolic defects, it has been customary to consider most if not all of this group of diseases to be inherited. A brief review of the genetic factors involved in the disturbances of lipid metabolism with particular reference to those conditions involving the nervous system therefore seems appropriate.

XANTHOMATOSES

Among the clinically diverse group of diseases characterized by a primary abnormality of lipid metabolism, the varieties most frequently encountered are the xanthomatoses. The terminology and classification of this group of related entities has been rather complex and somewhat confused in the older literature [illegible]

[illegible] an excellent discussion of the clinical considerations leading to this classification.

I. Hypercholesteremic xanthomatoses
- A. Essential hypercholesteremic xanthomatosis
  - Xanthelasma, xanthoma tuberosum et planum, tendon xanthoma, xanthoma of blood vessels, familial hypercholesteremia
- B. Xanthomatosis secondary to liver disease
  - Xanthomatous biliary cirrhosis and others
- C. Hypercholesteremia in hypothyroidism

II. Hyperlipemia with secondary eruptive xanthoma
- A. Idiopathic hyperlipemia
  - 1. Idiopathic hyperlipemia [illegible]
- B. [illegible]
  - 1. Untreated diabetes mellitus
  - 2. Chronic pancreatitis

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defects, or psychosomatic disorders, and whether disintegration of the adult personality under stress revives earlier and even primitive ways of reacting to tension.

It is hoped that with the focus of research on the aspects of differentiation in the use of body and its equipment as it reacts to internal stimuli and to the impact of environmental influence, both at rest and under stress, new clues will be furnished which will help explain personality development of both the so called "normal" as well as of the deviant individual.

DISCUSSION

President Hooker: *Dr. Russell Meyers of Iowa City asks Dr. Senn*: What does Dr. Senn mean by "emotion" and by what criteria does he distinguish this from intelligence?

Dr. Milton J. E. Senn (Closing): Again we can get into an involvement of semantics. For simplicity I think of emotions as feeling states—anger, love, hate—as opposed to intelligence which I consider the capacity and ability to understand, learn, cogitate, remember, think and use knowledge as one needs to for the further enhancement of one's development and usefulness in society.

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and combinations of visible lesions Xanthomatous involvement of blood vessels, especially the coronary arteries, and of the intima of the heart have been frequently reported The symptomatology is thus quite varied, some patients having no symptoms, some with painless nodules in the skin some with chronic fatigue, others with angina pectoris, and some dying suddenly of coronary thrombosis

The basic identity of these varied clinical manifestations is demonstrated by three points (a) histologic similarity of lesions, (b) elevated serum cholesterol in all types, (c) occurrence of different clinical varieties in members of the same family This last point may be illustrated by the pedigree in figure 47

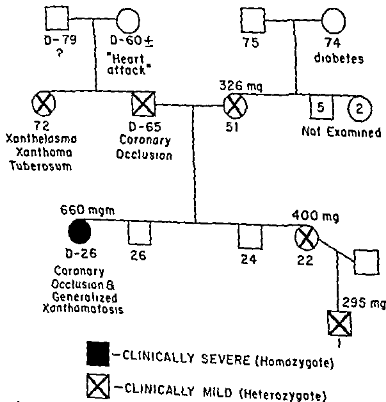


Fig 47 Essential familial xanthomatosis Pedigree described in text Numbers below symbol refer to age when examined or age at death. Numbers above symbols refer to serum cholesterol levels

3 Von Gierke's disease (glycogen storage)
4 *Lipid nephrosis*

III Normocholesteremic xanthomatoses
 A Eosinophilic xanthomatous granuloma
  1 *Eosinophilic granuloma of skin*
  2 Diabetes insipidus and xanthoma disseminatum
  3 Eosinophilic granuloma of bone
  4 *Schüller Christian syndrome*
  5 Generalized normocholesteremic xanthomatosis
 B Xanthoma cells in inflammatory tissue and tumors
 C *Supplement*
  1 Lipoid proteinosis
  2 Necrobiosis lipoidica diabeticorum

ESSENTIAL HYPERCHOLESTEREMIC XANTHOMATOSIS

As the name is intended to imply, this condition is characterized by an *increase in the total cholesterol in the serum, very frequently* with the formation of xanthomata in various tissues Although the total cholesterol content of the serum may be increased to several times its normal value the ratio of free cholesterol to cholesterol esters remains normal with about 70 to 75 per cent of the total representing the esters This may be accompanied by a slight increase in lecithin, usually expressed by a high value for total phospholipids but it is emphasized that increase in the neutral fat of the serum is not a feature of the disease The serum therefore remains translucent or slightly opalescent, but is never creamy or hyperlipemic Histologically, the hypercholesteremic type of xanthoma is characterized by the appearance of foam cells in the earliest stages of the lesions found in a vascular fibrotic tissue consisting of fibroblasts histiocytes and endothelial cells with a few lymphocytes and polynuclear cells The lesion also presents a special kind of giant cell known as the Touton cell with several nuclei arranged in a circle about an opaque cytoplasm This is in contrast to the picture in the normocholesteremic xanthomata in which proliferation of histiocytes and accumulation of eosinophiles occurs early with foam cells being added only late in the evolution of the lesions

Clinically the condition is quite variable with yellowish xanthomatous plaques or nodules in skin or subcutaneous tissue being most frequently noted Xanthelasma palpebrarum is common, and may frequently be unassociated with any other symptoms and accompanied by high normal or moderately elevated serum cholesterol values Other varieties include both discrete nodular and flat skin lesions usually found on the extensor surfaces of the extremities near joints and masses arising from tendons Several special descriptive names have been applied to the varying types

involvement, while 3 additional children had hypercholesteremia, one with mild cutaneous lesions while only 2 children had normal cholesterol values. The parents were second cousins and the father had hypercholesteremia, the mother presented a normal cholesterol on one determination, but 5 of her 7 half sibs had elevated values. Wilkinson, Hand and Fliegelman (59) made a careful study of a large family with clinical and biochemical examinations of 159 individuals in 4 generations. They present evidence suggesting that simple hypercholesteremia represents the heterozygous state of the gene and that patients with severe xanthomatosis represent the homozygous state of the same gene. This theory appears to have much to recommend it, but additional careful studies of large family groups are still needed for complete confirmation. From other studies it would appear that minor skin manifestations such as xanthelasma palpebrarum and small nodules about the fingers may also represent the heterozygous state of the gene. The evidence suggests that the very severe cases may be homozygous, but further data are needed to demonstrate a consistent correlation of clinical pattern and genotype.

IDIOPATHIC FAMILIAL HYPERLIPEMIA

This is a rare syndrome occurring in children first described by Buerger and Grütz (6) characterized by marked increase in neutral fat in the serum. Thannhauser (54) suggests that the condition may represent a functional disorder of capillaries causing retention of neutral fat in the blood. The patients may present skin lesions of a xanthomatous type and usually a moderate hepatosplenomegaly. Crises may occur with attacks of abdominal pain, tenderness and rigidity, vomiting, fever, leukocytosis and sometimes collapse. Such attacks may be mistaken for a surgical emergency. Such attacks occur with very high serum levels of total lipids, frequently over 8 g per 100 cc of serum (normal 0.5 to 0.8 g). The abdominal symptoms may be due to sudden distention of the liver and spleen, which undergo noticeable enlargement during such episodes. These crises usually terminate spontaneously in one to four days with fall of serum lipids to levels frequently in the range of 2 to 4 g. The condition should be differentiated from the idiopathic hyperlipemia of adults, which has few symptoms, usually those of xanthomatous skin eruptions, and which shows no familial incidence.

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while a brother (II 2) died at age 65 of a coronary occlusion, having had angina pectoris for several years previously. His serum cholesterol level was not determined. This man's wife (II-3) was examined at age 51 and was normal except for a serum cholesterol level of 396 mg, entirely asymptomatic. The oldest daughter (III 1) of this couple died at age 26 years presenting generalized xanthomatous involvement, the terminal event being coronary occlusion which was shown by autopsy to be due to xanthomatous lesions of the coronary vessels. Her two brothers were not available for examination, but a younger sister was found to have a serum cholesterol level of 400 mg, although she was without symptoms. Serum cholesterol determinations on this woman's only child gave values of 118 mg at age 10 days, 214 mg at age 3 months, and 295 mg at age 12 months.

We thus have xanthelasma of the eyelids, xanthoma tuberosum, coronary artery disease due to xanthomatosis and asymptomatic hypercholesteremia occurring in a closely related family group. Similar combinations within families have been previously reported, notably by Müller (36) who described 17 similar families and called particular attention to the high incidence of heart disease, especially with coronary artery insufficiency, in such families.

For more than half a century it has been recognized that there is an inherited form of xanthomatosis. As early as 1908 Gossage (17) summarized 7 families from the literature, pointing out that the ratio of affected to normal persons in these sibships was 1:1. A dominant type of transmission was suggested, but with early recognition that apparently normal individuals might transmit the abnormality to their children. It was later noted by several investigators that high serum cholesterol levels were frequently found among apparently normal parents and sibs of affected patients (31, 32, 46, 55). Svendsen (53) studied the serum cholesterol levels in 34 clinically normal relatives of a patient with xanthoma tuberosum, finding elevated levels in 16 relatives following a regular dominant pattern for 3 generations. He suggested that the hypercholesteremia itself was due to a dominant gene. Similar data were collected by Boas, Parets and Adlersberg (4) in 37 families of patients under age 50 with coronary artery disease, and analysis of these data by Stecher and Hersh (52) also suggested a simple dominant mechanism for the elevated serum cholesterol. Polano (41) had previously suggested a two-gene mechanism to explain the wide clinical variability noted, suggesting that one dominant gene determined hypercholesteremia while a second gene controlled cholesterol deposits in the clinically recognized xanthomata.

It is of further interest that observations were also made of hypercholesteremia in both parents of patients with severe forms of xanthomatosis. Sperry and Schick (51) reported an 11 year-old-boy with extensive changes

out of 9 children had severe xanthomatosis and died suddenly of [illegible]

involvement, while 3 additional children had hypercholesteremia, one with mild cutaneous lesions while only 2 children had normal cholesterol values. The parents were second cousins and the father had hypercholesteremia, the mother presented a normal cholesterol on one determination, but 5 of her 7 half sibs had elevated values. Wilkinson, Hand and Fliegelman (59) made a careful study of a large family with clinical and biochemical examinations of 159 individuals in 4 generations. They present evidence suggesting that simple hypercholesteremia represents the heterozygous state of the gene and that patients with severe xanthomatosis represent the homozygous state of the same gene. This theory appears to have much to recommend it, but additional careful studies of large family groups are still needed for complete confirmation. From other studies it would appear that minor skin manifestations such as xanthelasma palpebrarum and small nodules about the fingers may also represent the heterozygous state of the gene. The evidence suggests that the very severe cases may be homozygous, but further data are needed to demonstrate a consistent correlation of clinical pattern and genotype.

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had normal levels, while the mother and sister had levels slightly above the usually accepted normal limits. In the family described by Harslof (19) 3 brothers presented clinically severe forms of the disease, one dying at age 27 and one at age 8 years. The mother and 2 sisters who were apparently normal clinically presented slight elevation of total lipid and neutral fat content of the serum. The father was found to have an elevation of both total lipids and serum cholesterol, with xanthelasma palpebrarum. In another family reported by Chapman and Kinney (7) the serum fatty acid levels were normal in 4 sibs and both parents of an affected male who died at age 21 months. With the exception of the two cases mentioned where the mothers showed questionable or slight elevations of serum lipids, the few cases so far described seem to present a familial incidence only within a single sibship of the type expected with simple recessive inheritance. However, the demonstration of asymptomatic lipid elevations in normal relatives raises the question of a possible 'carrier state' (37). More data are needed, particularly of families where biochemical examination of relatives has been done, before the genetic mechanism may be defined exactly, but evidence so far suggests an autosomal recessive gene.

OTHER XANTHOMATOSES

With the exception of the fact that xanthomatous skin lesions may occur as a symptom of secondary hyperlipemia in uncontrolled diabetes mellitus and in von Gierke's disease, there is no definite evidence to implicate hereditary factors in the etiology of xanthomatoses other than the two types discussed above. Although several authors have included the Hand-Schüller-Christian syndrome in listings of hereditary metabolic defects, sometimes suggesting recessive inheritance, we have found no evidence to support this suggestion. Clinical reports of multiple cases of the Hand-Schüller-Christian syndrome within sibships seem to be lacking. Recent work has demonstrated that this syndrome is apparently not a separate disease entity but should be regarded as a special variant of the eosinophilic granuloma group. The studies which have clarified this situation have been reviewed by Thannhauser (54).

GAUCHER'S DISEASE

Gaucher's disease is characterized by an intracellular defect of lipid metabolism resulting in the formation and accumulation of the cerebroside kerasin in the cells of the reticulo-endothelial system. Kerasin may not be demonstrated in the circulating blood, and the serum lipid determinations are usually within normal range. Pathologically, a certain diagnosis may be made by demonstration of the typical Gaucher cell in bone marrow

lymph nodes, or other material and at autopsy these cells are found widely in liver, spleen lymphatic and marrow tissue, and often in the brain

The condition is usually found in children, 43 per cent of the cases tabulated by Hoffman and Makler (22) being under age 12 years and 17 per cent under the age of one year Delange (11) and Kohne (29) have described cases beginning in infancy as a special malignant form characterized by brain changes and neurologic signs The clinical course is thus subject to variation but usually the onset is insidious with marked enlargement of the spleen followed by liver and lymph node enlargement Bone pain which may be acute and severe is not infrequent and being often

frequent late sign Moderate anemia and leukopenia are usual, and a tendency to hemorrhage and easy bruising is common There is a correlation between severity of the disease and the age of onset with the cases with early onset proceeding rapidly to early death while those with late onset pursue a more benign course and may survive several years Death is usually by intercurrent infection

Gaucher s disease has long been regarded as familial and there are numerous reports of multiple cases within sibships the first of these being given by Collier (9) in 1895 As many as five cases have been described in one sibship (60) Cases in five related sibships of a negro family, with the parents of all five sibships being consanguineous have been described by Herndon and Bender (20) The condition is due to an autosomal recessive gene homozygotes being affected

NIEMANN PICK S DISEASE

The syndrome which was first described clinically by Niemann and characterized pathologically by Pick also represents an intracellular defect of lipid metabolism There is an accumulation and retention of sphingomyelin a diaminophosphatide in histiocytes and reticular cells also frequently involving epithelial and mesenchymal cells late in its course The glia cells of the

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histologic feature is the

Niemann Pick cells which are large pale foam cells of characteristic appearance and which involve practically all organs

The disease usually appears in infancy but is insidious in onset The infants may develop normally for weeks or months or may do poorly from birth They gradually stop eating and begin to lose weight and the abdomen

becomes enlarged. The liver and spleen become markedly enlarged and the patient appears to be dehydrated and emaciated. Lymphadenopathy occurs in about half the patients, and a yellowish brown pigmentation may occur on the extensor surfaces of the extremities in about one third of cases. A mongoloid expression is frequently noted, and the infant loses the ability to sit up or hold up the head. Motor power is lost usually without reflex changes, although about one fifth of patients develop rigidity and hyperreflexia and nystagmus occurs in one eighth (57). In about 60 per cent of cases a cherry red to reddish brown spot surrounded by a grayish zone is found at the fovea centralis. The optic disc may be pale or atrophic and blindness is a frequent late sign. There is rapid mental deterioration and the child may become idiotic. Vomiting is frequent and fever may appear in the late stages. Death usually occurs within a few months of inanition or intercurrent infection. In his summary of case reports in the literature Videbaek (57) noted that 33 per cent of patients died during the first year and an additional 43 per cent during the second year.

Niemann-Pick's disease is certainly rare, as only 75 to 80 cases have been described. Videbaek (57, 58) accepted as satisfactory the diagnostic data on 73 cases. The sex incidence was equal, there being 34 males and 35 females, the rest being of unreported sex. The condition is apparently more frequent among persons of Jewish ancestry, as 29 patients are reported to be Jewish, 26 non-Jewish, and in 18 cases the race is not reported. A familial incidence has been reported with certainty in at least 10 families, 9 of these presenting 2 affected sibs and in one family 3 children were affected. In at least 4 additional families there is presumptive evidence of affected sibs, although the diagnosis was not proved. Thus in nearly one third of cases there is a history of one or more affected sibs. The infantile form of Niemann-Pick's disease has not been described in more than one generation of a family. From the data available it seems safe to conclude that a rare recessive gene is responsible for this condition, the homozygotes being affected and heterozygotes being apparently normal.

In addition to the infantile form of Niemann-Pick's disease there is also a much rarer form occurring in adults. At least two clinically proved cases have been described in children at age 8 years and there are one or two reports concerning adults that are a bit doubtful clinically. However, unquestioned cases in two brothers aged 29 and 33 years were described by Pfändler (40). One brother died of accidental rupture of an enlarged spleen, and the diagnosis of Niemann-Pick's disease was adequately proved at autopsy. The second brother entered a hospital 2 years later with hepatosplenomegaly, slight jaundice, dyspnea, ankle edema, polycythemia, and an acute bronchitis and died in heart failure. The cardiac decompensation and polycythemia were probably the result of extensive

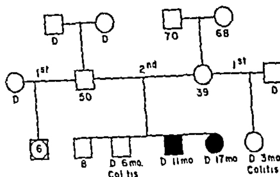


Fig 40 Niemann-Pick's disease Pedigree of family with two cases in one sibship The affected children are issue of the second marriage for both father and mother Half sibs were normal parents were not consanguineous

pulmonary infiltration with Niemann-Pick cells There was chemical demonstration of sphingomyelin storage and the diagnosis seems proved beyond question In the family of these patients 3 sibs had died in infancy of unknown causes and one sister died at age 11 Three sibs refused examination Two brothers had enlargement of liver and spleen with low serum cholesterol and high fatty acids Two sisters and one brother showed minor abnormalities of serum cholesterol and fatty acids described by Pfandler as microsymptoms In addition a cousin and 4 nephews and nieces showed minor serum lipid abnormalities The possibility of a dominant gene is suggested by Pfandler with the minor variations representing a carrier state This viewpoint has been attacked by Thannhauser (54), who points out that a diagnosis of Niemann Pick's disease has been proved only for the two brothers dying of the disease As this family is at present unique judgment must be deferred Careful biochemical investigation of apparently normal relatives should be carried out in any similar families that may be discovered

AMAUROTIC IDIOCY

The terms amaurotic idiocy and cerebromacular degeneration are applied to a group of at least two and perhaps four clinical syndromes that are similar in many respects and probably based on a lipid disturbance in cells of the central nervous system The four groups usually described are as follows

1 Infantile amaurotic idiocy (Tay Sachs disease)
2 Late infantile form (Bielschowski)
3 Juvenile amaurotic idiocy (Spielmeyer Vogt disease)
4 Late juvenile form (Kufs)

Tay-Sachs disease (infantile amaurotic idiocy) may rarely appear

becomes enlarged The liver and spleen become markedly enlarged and the patient appears to be dehydrated and emaciated Lymphadenopathy occurs in about half the patients, and a yellowish-brown pigmentation may occur on the extensor surfaces of the extremities in about one-third of cases A mongoloid expression is *frequently noted, and the infant loses the* ability to sit up or hold up the head Motor power is lost usually without reflex changes, although about one-fifth of patients develop rigidity and *hyperreflexia and nystagmus occurs in one eighth (57) In about 60 per cent* of cases a cherry-red to reddish-brown spot surrounded by a grayish zone is found at the fovea centralis The optic disc may be pale or atrophic, and blindness is a frequent late sign There is rapid mental deterioration and the child may become idiotic Vomiting is frequent and fever may appear in the late stages Death usually occurs within a few months of inanition or intercurrent infection In his summary of case reports in the literature, Videback (57) noted that 33 per cent of patients died during the first year and an additional 43 per cent during the second year

Niemann-Pick's disease is certainly rare, as only 75 to 80 cases have been described Videback (57, 58) accepted as satisfactory the diagnostic data on 73 cases The sex incidence was equal, there being 34 males and 35 females, the rest being of unreported sex The condition is apparently more frequent among persons of Jewish ancestry, as 29 patients are reported to be Jewish, 26 *non-Jewish, and in 18 cases the race is not reported* A familial incidence has been reported with certainty in at least 10 families, 9 of these presenting 2 affected sibs and in one family 3 children were *affected In at least 4 additional families there is presumptive* evidence of affected sibs, although the diagnosis was not proved Thus in nearly one-third of cases there is a history of one or more affected sibs The *infantile form of Niemann Pick's disease has not been described in more* than one generation of a family From the data available it seems safe to conclude that a rare recessive gene is responsible for this condition, the *homozygotes being affected and heterozygotes being apparently normal*

In addition to the infantile form of Niemann-Pick's disease there is also a much rarer form occurring in adults At least two clinically proved cases have been described *in children at age 8 years and there are one* or two reports concerning adults that are a bit doubtful clinically However, unquestioned cases in two brothers aged 29 and 33 years were described by Pfandler (40) *One brother died of accidental rupture of an enlarged* spleen, and the diagnosis of Niemann Pick's disease was adequately proved at autopsy The second brother entered a hospital 2 years later with hepatosplenomegaly, slight jaundice, dyspnea, ankle edema, polycythemia and an acute bronchitis, and died in heart failure The cardiac decompensation and polycythemia were probably the result of extensive

Tay-Sachs and Spielmeyer-Vogt types. It begins at age 3 or 4 years and runs a slower course than the infantile variety. The symptoms are similar, but with ataxia and other cerebellar signs which are not demonstrable in the infantile cases. The cherry spot at the macula is not found, but there may be optic atrophy and pigmentation of the retina.

The late juvenile (or adult) type described by Kufs (30) is also rare. It usually begins between age 15 and 25 years and progresses very slowly. Mental deterioration and convulsions appear early, followed by tremor, muscular rigidity and cerebellar type ataxia. The patients usually have no loss of vision but retinitis pigmentosa has been described in relatives. A summary and comparison of the clinical features of the disease in the four age groups is given by Rothstein and Welt (43).

Both Tay-Sachs and Spielmeyer-Vogt types of amaurotic idiocy have been considered familial diseases since the earliest cases were described. A careful genetic study of the juvenile variety was made by Sjogren (47) showing the disease to be due to a simple recessive gene, homozygotes being affected. Among 145 sibships containing affected children, the parents were first cousins in 23 instances (16 per cent) and related in other ways in 26 families (18 per cent). In all cases the parents were normal. The published data regarding Tay-Sachs disease were summarized by Slome (48), this analysis also producing satisfactory evidence for action of a simple recessive gene. Tay-Sachs disease has been described in two sets of monozygotic twins, both twins being affected in both pairs (28, 26). Concordance in disease in monozygotic twins offers additional evidence of genetic causation.

The evidence also suggests that the recessive genes responsible for Tay-Sachs and Spielmeyer-Vogt's diseases are not ... [illegible]

... from 1 to 12 months and age at death from 7 to 30 months, while in the Spielmeyer-Vogt type age of onset ranged from 2 to 11 years and age at death from 9 to 24 years. Most important, in spite of the large number of multiple cases within sibships, no instances have been encountered of occurrence of both the Tay-Sachs and Spielmeyer-Vogt types within one family. It seems likely that the pathologic changes and basic defect in lipid metabolism may be very similar or identical in all forms of amaurotic idiocy, as Globus (16) suggests, but that the observed clinical differences justify separation into the Tay-Sachs and Spielmeyer-Vogt types, which are probably genetically distinct. The so-called transitional types described by Bielschowsky and by Kufs have not been adequately studied genetically. Any speculation as to whether these types may be caused by additional genes or whether

within the first two weeks of life but more commonly has its onset between the 4th and 7th months The infant at first becomes listless does not feel well, and motor reactions previously acquired become weaker and then lost There is a slowly progressive loss of muscle power until the infant becomes completely helpless with soft and flabby muscles It will usually be noted that the child has become blind but unusual acuity of hearing may appear, with the child starting at the slightest noise Later muscular spasticity and hyperreflexia may appear, with muscle twitchings and convulsions and decerebrate rigidity has been often observed There is weight loss and emaciation and bulbar palsy eventually makes normal feeding impossible The disease is always fatal the majority of cases dying between the 2nd and 3rd years The classical cherry red spot at the macula is seen in most cases but may sometimes be absent

Detailed descriptions of the pathologic changes have been given by several investigators and the findings are summarized by Ford (13) The brain is frequently hard or leathery in consistency The ganglion cells throughout the entire central nervous system are swollen and the cytoplasm appears finely granular or hyaline Special stains demonstrate that the swelling and distortion of cells is due to accumulation of lipid droplets Large balloon like swellings appear on the dendrites Demyelination appears which seems to be secondary to cell destruction The microglia and astrocytes undergo proliferation and distention The vascular system remains unchanged The macular changes are due to an identical process in the retinal ganglion cells with secondary optic nerve degeneration

The clinical course of the juvenile variety Spielmeyer Vogt disease is similar but characterized by later onset and slower progression The onset is between 3 and 10 years of age most commonly between 5 and 6 years Loss of vision is usually the first sign and according to Sjogren (47) may be considered the first stage of the disease and may last about two years The second stage is characterized by tonic and clonic convulsions and by mental changes largely irritability loss of emotional control and personality changes Definite mental deterioration follows with progression to dementia Muscle rigidity and tremors appear and progress to paralysis Athetoid movements may occur Death occurs within 10 to 15 years usually in convulsions or from intercurrent infection The retinal lesions in the juvenile form are often more diffuse than in the infantile type and a dark brown pigment is often formed In some cases the retinal lesion may be quite diffuse with pigmentation resembling that in retinitis pigmentosa Secondary atrophy of the optic nerve occurs with rapid loss of vision

The late infantile (or early juvenile) form of amaurotic idiocy described by Bielschowski is quite rare and seems to be intermediate between the

open as Sachs (1939) suggested until more extensive biochemical and genetic data are available

GARGOYLISM

Gargoylism sometimes known as the Hunter Hurler syndrome or as lipochondrodystrophy, is a disease of children usually characterized by grotesque appearance dwarfing, mental retardation and bone changes Although it is generally agreed that the condition is based on a metabolic disturbance there is some question as to whether the *primary* defect is in lipid or in carbohydrate metabolism

The earlier writers usually agreed in classing gargoylism among the lipidoses as the autopsy material consistently demonstrated abnormal storage of a material giving some lipid reactions to stains Widespread defects in collagenous tissues were demonstrated, these *tissues containing* cells of presumed fibroblast origin enlarged by deposited material Similar changes were often described in ganglion cells of the brain sometimes

... material was found in practically all tissues except nerve cells Brante suggests that the lipid disturbance may be secondary to the abnormal formation and storage of the mucopolysaccharides

Clinically the syndrome includes mental defect and multiple deformities of bone *often resulting* in dwarfing limitation of extension of the extremities skull *deformities* kyphoscoliosis or lordosis shortness of the neck, and characteristic radiologic findings *The* grotesque facies is characteristic Additional frequent findings include hepatosplenomegaly, corneal clouding, hypertrichosis hernia and deafness Even in typical cases any one feature may be absent and *the diagnosis* is based *on* the coexistence of several features A *forme fruste* has been *described with* milder abnormalities and Jervis (25) has discussed the *diagnostic problems encountered* Lindsay (33) has emphasized the frequency *of* cardiovascular involvement *reporting* evidence of this in 11 *of* 16 *patients* examined with 4 of 8 fatal cases dying of cardiac failure

Gargoylism was promptly recognized as a familial condition *In 1942* Halperin and Curtis (18) collected *data on 40* sibships from the literature containing 57 affected children 32 males ...

... ex

... system and *of*

they represent modified varieties of one of the two basic types would be premature.

RELATIONSHIP OF TAY-SACHS' DISEASE AND NIEMANN-PICK'S DISEASE

There has been considerable discussion concerning a possible relationship between the Tay-Sachs variety of amaurotic idiocy and Niemann-Pick's disease, and the situation is still not entirely clear. Clinically they are distinguished by the confinement of abnormality to the central nervous system in Tay-Sachs' disease and the presence of both neurologic and general visceral involvement in Niemann-Pick's disease. Rothstein and Welt (43) discussed the problem at length and concluded that this is the only safe basis of clinical distinction of the two conditions. This is at best an arbitrary distinction but has been useful clinically.

The points of similarity that have been widely discussed are as follows. The two clinical pictures may be quite similar, with age of onset, speed of progress and time of death being similar. Both seem to occur with increased frequency in the Jewish race, suggesting a higher gene frequency here than in other ethnic groups. Retinal involvement with the cherry spot at the macula and blindness occurs in 60 per cent of cases of Niemann-Pick's disease. Although Rintelen (42) holds that the cherry spot is not pathognomonic but is the result of decreased transparency secondary to ganglion cell destruction from any cause, it must be emphasized that the cherry spot has not been described in any disease other than the two under consideration. However, Rintelen (42) feels that the retinal changes in Tay-Sachs and Niemann-Pick's diseases may be distinguished histologically. The close similarity or identity of the histologic changes in the brain has been repeatedly emphasized (43). Thannhauser, Benotti and Reinstein (56) have performed chemical studies on a brain of each group and hold that the stored lipids are chemically different, sphingomyelin being increased in Niemann-Pick's disease but not in Tay-Sachs. Klenk (27) has isolated a new group of lipids from a Tay-Sachs brain called gangliosides, demonstrating these to be considerably elevated in Tay-Sachs and only moderately elevated in Niemann-Pick's disease.

From the genetic viewpoint an important item of evidence is the fact that cases of Tay-Sachs and Niemann-Pick's diseases have been reported in sibs (12, 50). Thannhauser (54) raises doubt concerning the diagnosis in some cases because of the lack of detailed chemical analyses and expresses the opinion that the lipid disturbance is basically different in the two conditions. In the writer's opinion this question remains unsettled. It should be pointed out that the reported chemical differences rest on studies of only one or two brains in each condition. The possibility of genetic identity of Tay-Sachs and Niemann-Pick's diseases must be kept

may be summarized by stating that no differences related to genetic pattern were found for 11 of the 14 signs tested, but three gave positive results The signs showing correlation with genetic pattern were corneal clouding dwarfism and deafness The frequencies of these signs in the three groups of patients are given in table 16, together with the frequencies of two additional signs showing no correlation, hepatosplenomegaly and limitation of extension of joints of the extremities

It is thus seen that corneal clouding has not been described in any case that may be identified as sex linked by pedigree, while it is found in 81 per cent of those that may be identified as recessive Dwarfing is less frequent in the sex linked group than in the recessive group, while the

minimum values as any characteristic not specifically mentioned was recorded as not present Corneal clouding particularly may have been overlooked as many patients in the recessive and mixed groups were not examined with the slit lamp It is fortunate that particular attention was given to corneal examination in the sex linked families

The question of consanguinity of the parents of affected children is of interest in connection with any uncommon recessive gene The frequency of consanguinity should be increased among parents of the recessive group, but no increase would be expected in the sex linked group Among the 189 sibships studied the parents were reported to be kin in 14 families (7 4 per cent) In six instances the parents were first cousins and in 8 instances more distantly related or not specified exactly Twelve of the resulting sibships contained an affected female and may be recognized as recessive Two additional sibships contained only one affected child, a male and would be included in group 2 in table 16, but in both instances the patients presented corneal clouding Thus all 14 consanguineous

TABLE 16

Frequency of clinical signs related to genetic pattern

	Group 1 Recessive cases n = 96	Group 2 Males only mixed cases n = 130	Group 3 Males, sex linked pedigree n = 21
	per cent	*per cent*	*per cent*
Corneal clouding	81 3	49 [illegible]	0
Dwarfing	72 9	47 7	33 3
Deafness	5 2	17 7	42 9
Hepatosplenomegaly	72 9	72 3	81 0
Joint limitation	89 6	89 2	66 7

Lenz, also obtaining satisfactory agreement with the autosomal recessive hypothesis. In examining these data it was noted that the sex ratio was unequal, there being 94 affected males and 52 affected females giving a chi square value of 11.6. A reason for this significant excess of affected males was sought, and in the literature seven families were found with family histories giving clear evidence of the existence of a sex-linked recessive gene (8, 14, 24, 34, 35, 38, 49). It will be noted that all but one of these have appeared since the date of the summary by Jervis.

It thus seemed apparent that there must be two genetically distinct forms of gargoylism, one due to an autosomal recessive gene and the other due to a sex-linked recessive gene. The literature was reviewed and reports were found concerning 252 cases, 168 of these being males, 79 females and 5 of unreported sex. This gave an even greater excess of males than that observed by Jervis ($\chi^2 = 32.1$, $p < 0.0001$). The calculations of the corrected ratio of affected to normal children in complete sibships according to the methods of Bernstein and Lenz were repeated confirming the findings of Jervis. It is apparent, however, that a ratio of one affected to three normal children would be approximated by a series of families where the affecteds are those homozygous for a recessive gene and also by a series where part or even all of the affecteds were males exhibiting a sex-linked defect. The heterogeneity of such mixed data would be recognized by an aberrant sex ratio with an excess of affected males or by pedigree examination. If it should be assumed that all of the excess of affected males (89 cases) is due to inclusion of sex-linked sibships in the data, one would conclude that approximately one third of the total cases of gargoylism are due to sex-linked genes and two thirds due to autosomal recessive genes.

Because of the rather wide variability of clinical findings in this syndrome a tabulation of clinical signs was made to check for possible correlation between genetic pattern and clinical pattern, such as Allan (1, 2) has demonstrated in peroneal atrophy and in retinitis pigmentosa. The presence or absence of 14 clinical signs was tabulated for a series of 247 patients. The patients were separated into three groups as follows. Group 1 consists of all patients, both male and female, in sibships containing at least one female. It was felt that all of these are certainly simple recessive cases and 96 patients fall into this group. Group 2 consists of only male patients in families with only one or two affected males and no affected females. This group represents a mixture of recessive and sex-linked cases that cannot be identified as to genetic mechanism by pedigree alone and contains 130 cases. Group 3 consists of 21 affected males in the seven families giving clear evidence of sex linkage on the basis of pedigree data. The detailed analysis of these groups is presented elsewhere (21). The results

2 Idiopathic familial hyperlipemia is rare, the affected children being homozygous for an autosomal recessive gene Asymptomatic elevations of total serum lipids have been reported in some relatives, raising the possibility that the heterozygous state may be recognized by chemical study

3 There is no convincing evidence that genetic factors are of importance in the etiology of the Hand-Schüller Christian syndrome

4 Gaucher s disease is due to a rare autosomal recessive gene, affected individuals being homozygous

5 Niemann Pick's disease also represents the homozygous state of a rare autosomal recessive gene

6 Amaurotic idiocy must be subdivided into at least two groups, the infantile or Tay Sachs type and the juvenile or Spielmeyer Vogt type. Both types represent the homozygous state of a rare recessive autosomal gene but the evidence suggests that two different genes are involved, one [illegible]

[illegible] recessive gene and the other due to a sex linked recessive gene The sex-linked form is characterized by absence of corneal clouding infrequent [illegible] ed

DISCUSSION

Dr C Glen King (New York N Y) I would like to ask whether Dr Herndon has found an opportunity to associate either experimentally or from [illegible]

Dr J P [illegible]

President Hooker We have a question from the floor from Dr [illegible] Galesburg State Re[illegible] showed [illegible] galactose [illegible] on this [illegible] this disease can be explained

matings were in families where autosomal recessive genes are probably involved and none are reported in families with the sex linked type.

Four families were encountered containing twin pairs with one or both affected. Cordes and Hogan (10) reported two sets, only one of each pair being affected. One set is clearly dizygous, the affected twin being male and the normal partner female. In the other set both twins are female but no data regarding zygosity are available. Nonne (39) reported a pair of twins, both females and both affected. It is stated that these twins resemble each other strongly but other evidence of monozygosity is lacking. Sartori (45) presents an additional dizygous pair, a male being affected and a female co-twin normal.

We therefore conclude that the syndrome of gargoylism may be divided into two genetically distinct varieties, one autosomal recessive and the other sex linked recessive. The reservation must be made that it is impossible to distinguish between a sex linked recessive and a sex limited dominant gene without examination of the offspring of affected males, and data critical for this point are lacking. In the absence of any data to support sex limitation it is assumed that the mutant gene is on the unpaired portion of the X chromosome. About two thirds of patients fall into the autosomal recessive group and about one third into the sex linked group. Clinically the sex linked group is characterized by absence of corneal clouding and with only one third of the patients being dwarfed but with about 43 per cent being deaf. In the recessive group corneal clouding and dwarfness are usual, each occurring in about three fourths of patients and with 98 per cent showing one or the other, while deafness is uncommon, occurring in only 5 per cent of patients.

SUMMARY AND CONCLUSIONS

A survey is made of the data available in the literature concerning hereditary factors in the etiology of the diseases of lipid metabolism. The following conclusions seem justified.

1. The groups of primary xanthomas characterized by elevation of serum cholesterol, including xanthelasma, xanthoma tuberosum et planum, tendon xanthoma, xanthoma of blood vessels and familial hypercholesteremia, are genetically only different manifestations of the same disease, here termed essential hypercholesteremic xanthomatosis. In the heterozygous state the responsible gene produces hypercholesteremia which may be asymptomatic or associated with minor xanthomatous manifestations but probably predisposes its carriers to atherosclerosis, especially of the coronary arteries. In homozygous state the gene causes the more severe forms of xanthomatosis, many of these patients having severe blood vessel involvement, often with early death by coronary artery thrombosis.

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DR C NASH HERNDON (Closing) I thank the discussants for their comments With regard to Dr King's question regarding the enzymatic basis, the work that is available in the literature, so far as I know, is quite fragmentary Most of it has been concerned with analyses of the abnormal lipids which are deposited within the nervous system or within the liver and spleen, and I am not aware of any serious work on the enzymes which gives any clear-cut idea as to just what is happening at the enzyme level

With regard to Dr Scott's question, again, I cannot give an answer as to just what the biochemical effect is on the nervous system, in most of these conditions Of course in Gaucher's, Niemann Pick's, and Tay Sach's disease, there is an anatomic disruption particularly with involvement of the ganglion cells With regard to gargoylism there is storage of an abnormal substance within the brain, and I assume that it is largely a physiological matter of disruption of the motor pathways by the abnormal storage material

With regard to Dr Schut's question on Gaucher's disease certainly, the metabolism does take an abnormal course The substance, kerasin, which is formed and which is associated with the glucose molecule, is an abnormal one It does not occur in normal brains in any appreciable amount and cannot be recovered from the blood even in affected individuals Certainly, it seems that some enzyme probably within the cell may be absent or misdirected resulting in formation of an abnormal substance which the body is unable to use and which it therefore stores within the cells

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CHAPTER XVI

PHENYLPYRUVIC OLIGOPHRENIA (PHENYLKETONURIA)

GEORGE A JERVIS

Phenylpyruvic oligophrenia, a condition characterized by mental deficiency and urinary excretion of phenylpyruvic acid was first described in 1934 by Folling (38) who reported 10 cases in Norway and established the basic biochemical features of the disease Shortly thereafter, cases were reported in England (81), France (90), U S A (49) and later, in many other countries Table 17 gives the number of cases thus far reported

The disease originally known as *imbecillitas phenylpyrouvica* (38), was later denoted phenylpyruvic oligophrenia (49) in order to emphasize [illegible]

into line with that of other comparable biochemical abnormalities such as cystinuria and alkaptonuria The two terms *phenylpyruvic oligophrenia* and phenylketonuria are used interchangeably

The purpose of this presentation is to review the present knowledge concerning clinical biochemical, pathologic and genetic aspects of the disease This review is based on personal findings in some 226 cases, and on the data which have been accumulated in the literature during 20 years

INCIDENCE

The incidence of phenylketonuria may be assessed from the data on the frequency of the condition among institutionalized mental defectives These data are presented in table 18 The total percentage among 48,536 defectives is 0 64 However, it may be seen that there are considerable percentage variations among the various investigators

Aside from the size of the sample examined these variations may be explained by differences in the composition of the sample Since phenylketonurics are mostly low grade defectives surveys in institutions which contain large numbers of idiots will yield higher percentages Th[illegible]

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TABLE 18

Incidence of phenylketonuria among institutionalized defectives

Author	Reference	Country	Defectives examined	Number of phenylketonurics	Percentage
Jervis	50	U S A	20 300	161	0 79
Josephy	58	U S A	4 300	16	0 37
Frazier	43	U S A	3 000	10	0 33
Levy Perry	65	U S A	1 408	9	0 64
Ford	44	U S A	1 000	5	0 50
Munro	78	England	2 457	30	1 22
Bates	5	England	2 300	3	0 13
Cowie	33	England	553	15	2 71
Turpin Duchene	97	France	2 264	2	0 09
Rhein Stoeber	90	France	650	7	1 08
Delay et al	27	France	209	1	0 48
Lusso	69	Italy	2,010	1	0 05
Mazzei	73	Italy	310	1	0 32
Brugger	14	Switzerland	1 631	1	0 06
Følling et al	41	Norway	2 400	29	1 21
Larson	62	Sweden	1 388	8	0 58
Lassen	63	Denmark	840	8	0 95
Cantor	16	Australia	600	2	0 33
Ferreira	37	Brazil	471	1	0 21
Martin	70	French Canada	261	0	0 00
Meldicott	74	New Zealand	190	2	1 05
Totals			48 536	312	0 643

In Norway certain isolated groups of population show a high incidence of the disease (41)

If one accepts the figures of 0 64 per cent (table 18) as representative of the incidence of phenylketonuria in the defective population and 1 per cent the incidence of defectives in the general population, then the incidence of phenylketonuria in the general population may be assumed to be of the order of 6 per 100 000 (0 006 per cent) However th

was 1 22 per cent phenylketonurics in Munro's material (78), there examined the incidence of low grade defectives being about 0 2 per cent in the general population the incidence of phenylketonuria would be of the order of 2 4 per 100 000 The probability is that the real figure is somewhere between the two extremes of 0 002 per cent and 0 006 per cent, or of the order of 4 per 100 000 In the United States there would be, therefore, some 6 400 phenylketonurics

TABLE 17

Cases of phenylpyruvic oligophrenia

Author	Reference	Country	No patients
Jervis	50	U S A	226
Josephy	58	U S A	16
Levy-Perry	65	U S A	13
Frazier	43	U S A	10
Ford	42	U S A	5
Alvord, et al	2	U S A	5
Mautner Quinn*	71	U S A	5
Cohen Kozinn	18	U S A	2
Warthen, et al	100	U S A	2
Dann, et al	25	U S A	1
Munro	78	England	85
Cowie	22	England	17
Woolf	102	England	6
Bates	5	England	3
Bickel Gerrard	9	England	1
Rhein Stoeber	90	France	7
Delay, et al	28, 29, 30	France	4
Turpin, et al	96, 97	France	2
Brugger	14 15	Switzerland	4
Meister	73	Switzerland	2
Lepow	64, 77	Switzerland	1
Klein	60	Switzerland	1
Papiro	80	Italy	3
Lotti	67	Italy	3
Lusso	69	Italy	2
Andreani	3	Italy	1
Mazzei	72	Italy	1
Schrappe	92	Germany	4
Steinborn	95	Germany	1
Fölling, et al	41	Norway	41
Lassen	63	Denmark	9
Larson	62	Sweden	8
Cantor	16 17	Australia	8
Meldicott	74	New Zealand	4
Penrose	85	Canada	5
Coquet, et al	20	Belgium	2
Ferriera	37	Brazil	1

* The remaining patients of this series were previously reported by Jervis (50)

unknown in Jewish populations only one family having been reported (18), and in the Negro race in which only one case has been found (37) Finally, geographical distribution of the defective population examined might be of some significance In England, for instance, the disease is more frequent in Wales and Lancashire, and rare in the Home Counties (78)

TABLE 19

Distribution of I Q in 330 phenylketonurics

I Q	Below 10	11 20	21 30	31-40	41 50	51-60	61 70	Above 70
Number	1[illegible]	88	41	34	31	7	4	3
Per cent	37	26	12	10	9	2	1	0 9

found Over 90 per cent of the cases are fair haired and fair skinned with light blue eyes Striking instances of blond phenylketonurics in darkly pigmented people of Sicilian or Spanish descent have been reported (50, 96) It should be noted however, that dark-eyed, dark haired phenylketonurics are observed *occasionally* A case of a full blooded Negro has been reported (97) and another in a Puerto Rican child of mixed Negro-Spanish blood was personally observed Cowie and Penrose (24) studied spectrophotometrically the hair color in phenylketonurics as compared with siblings and other members of the family and were able to demonstrate a relative dilution The relationship if any of the defective pigmentation to the metabolic abnormality has not been determined, although the role of aromatic amino-acid including phenylalanine, in the formation of melanine pigments is known The claim that the lighter the complexion, the lower the I Q (7) could not be confirmed by personal observations The skin is usually soft smooth and fine in texture The patients show a tendency toward developing dermatitis (6 23 26, 29, 38 45 46, 79)

On neurological examination, over a third of phenylketonurics show no significant deviation from the normal In about another third, neurological signs are present which could be interpreted as somewhat abnormal, these include hyperactivity of the deep reflexes mild muscular hypertonicity, awkward gait slight tremors and occasional adventitious movements More marked neurological manifestations are found roughly in 30 per cent of phenylketonurics the posture is often stooped (pithecoid [illegible] the gait is [illegible]

hyperactiv [illegible]

absent Mo [illegible] and the reflexes are sluggish Tremors of the outstretched hands, occasionally diffuse to the whole body, may be present in this group and purposeless movements of hands, often similar in type to athetoid movements are observed These manifestations are usually stationary The presence of [illegible]

[illegible] eurological picture is that of

Sex distribution

Of 465 patients 228 (49 per cent) are males and 237 (51 per cent) females No significant difference is observed therefore in the sex distribution of phenylketonuria

CLINICAL SYMPTOMATOLOGY

Mental defect

All individuals excreting phenylpyruvic acid are apparently mentally defective Phenylketonuria in mentally normal individuals has not been reported however there are no surveys of large segments of normal populations with the exception of a personal unpublished examination with negative results of some 10 000 young healthy men in military service

The distribution of the intelligence quotient in 330 patients in whom exact psychometric data are available is seen in table 19 It may readily be seen that the majority of patients are of low grade intelligence No distinctive patterns are noticeable usually in the psychometric examination

Of considerable interest are the few cases of borderline and dull normal intelligence A patient described by Cowie (22) had an I Q of 76 on the Binet and 90 on the Porteus test In another case reported by Brugger (14) the I Q was 85 The patient described by Cohen et al (18) had an I Q of 69 and was able to support himself and his family A boy 7 years of age (personal observation) showed an I Q of 86 his sister also a phenylketonuric had an I Q of 20 showing that striking differences within the same family may occur

Progressive mental deterioration has been noted by some investigators (7 71) and the disease is classified in the group of progressive deteriorating conditions of the brain (7) However personal observation in a large number of cases over a period of many years shows that mental deterioration does not occur as a rule although in an occasional patient a moderate drop in I Q may be observed It has been claimed also that mental defect develops only after the first year of life (4 9) but no convincing evidence has been brought forward as yet in favor of this interesting hypothesis which would be of great importance in the therapy of the condition

General physical development is usually unimpaired Stunted stature is occasionally found (43 60) but considerably less frequently than among non phenylketonuric individuals of comparable mental level Gross physical defects are not commonly found In fact it is not unusual that phenylketonurics in infancy and childhood are singled out for their attractive features However widely spaced incisor teeth (23) epicanthus (49) pes planus (23) and partial syndactyly (23) are mentioned in single cases The head is often slightly reduced in size no characteristic skull shape is

TABLE 19

Distribution of I Q in 330 phenylketonurics

I Q	Below 10	11 20	21 30	31–40	41 50	51–60	61–70	Above 70
Number	122	88	41	34	31	7	4	3
Per cent	37	26	12	10	9	2	1	0 9

found Over 90 per cent of the cases are fair-haired and fair-skinned with light blue eyes Striking instances of blond phenylketonurics in darkly pigmented people of Sicilian or Spanish descent have been reported (50, 96).

was personally observed Cowie and Penrose (24) studied spectrophotometrically the hair color in phenylketonurics as compared with siblings and other members of the family and were able to demonstrate a relative dilution The relationship, if any, of the defective pigmentation to the metabolic abnormality has not been determined, although the role of aromatic amino-acid, including phenylalanine, in the formation of melanine pigments, is known The claim that "the lighter the complexion, the lower the I Q" (7) could not be confirmed by personal observations The skin is usually soft, smooth and fine in texture The patients show a tendency toward developing dermatitis (6, 23, 26, 29, 38, 45, 46, 79).

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similar in t

are usually

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cor

cer

... the neurological picture is that of

stationary severe cerebral palsy with diplegia, contractures and pyramidal signs.

A certain percentage of patients (not above 10 per cent) shows psychotic episodes characterized by restlessness, destructive and noisy behavior. In a patient, personally observed, who showed periodic psychotic episodes, no relationship could be established between psychotic behavior and excretion of phenyl derivatives.

No case of the disease was found in a survey of the congenital deaf (66).

Epilepsy is a common feature of phenylketonuria. In 418 patients in whom this symptom was looked for, 105 (25 per cent) had convulsions. The epileptic attacks are usually infrequent and occur mostly in infancy and childhood. Severe prolonged epilepsy is the exception. The electroencephalogram in patients is often abnormal (75), even in those showing no clinical epilepsy.

PATHOLOGICAL FINDINGS

Essentially negative findings in the central nervous system are reported in autopsies available in the literature (20, 58, 60, 62, 84) as well as in two biopsies (73). In one of these cases (84) there were numerous fibromata along several nerves, a finding which remains unique. Diffuse neuron cell lesions of the retrograde degeneration type are described in a case by Corsellis (19) and interpreted either as evidence of complicating pellagra or tentatively and with many reservations as connected with abnormalities of protein metabolism.

In contrast with these essentially negative findings are the lesions of myelin reported by other investigators. Alvord et al. (2) described demyelination of optic, cortico-spinal and cortico-ponto-cerebellar system in a 16 months old phenylketonuric. In another patient, 5 years old, there was light staining of myelin in the optic nerve and spinal cord. The examination of three adult cases showed demyelination and gliosis limited to the optic chiasma in one instance. Benda (7) in two cases (both adult patients) found striking demyelination of the central white matter as well as of the white matter of the cerebellum and spinal cord, with accumulation of myelin balls. This last finding was so marked in degree that the condition was compared to a storage disease ("macromolecular syndrome," 7).

Five cases of personal observation were studied for histological evidence of myelin changes. In four, all adults, no demyelination was found; in the fifth, a boy 3 years of age, there was some paleness of myelin in the temporal regions as compared with other regions of the centrum semiovale.

The interpretation of all these findings is not clear. It is possible that Alvord's (2) findings are the expression of a retarded myelination, but whether specific of, and due to, the metabolic disorder of phenylketonuria

is uncertain since little is known about myelination in severely retarded infants. Striking demyelination as described by Bendy (7) must be the exception since it was not observed in any other case reported. In this connection it is interesting to mention a personally observed phenylketonuric showing no neurological manifestations who at the age of 25 years developed a progressive disease characterized by motor deficit and mental deterioration. Post mortem the typical lesions of Schilder's disease were observed grossly. Whether this case represents a chance combination of the two conditions or is further evidence suggesting a tendency to myelin degeneration in phenylketonuria only additional observations will indicate.

It appears in conclusion from the data available thus far, that no definite statements can be made concerning morphological lesions of the central nervous system which underlie the striking mental retardation characteristic of phenylpyruvic oligophrenia.

Pathological findings outside the central nervous system are limited to scattered observations. Hypoplasia of pituitary and testicles (60), lack of chromophilic elements of the pituitary gland (7), fatty degeneration of the liver (23, 71) have been reported.

BIOCHEMICAL FINDINGS

Phenylpyruvic oligophrenia is characterized biochemically by the presence of abnormally high amounts of phenylalanine and its derivatives in the body fluids.

Phenylalanine can be demonstrated by various methods, including (1) the nitration method of Kappeler-Adler (59) and its various modifications (1, 10, 91), (2) microbiological assays (35), and (3) enzymatic conversion of the amino acid into the corresponding amine (98). Only the last method is specific for phenylalanine, the other two measuring also its deaminated derivatives which should be *removed by* extraction prior to the determination of the amino acid.

In the urine of phenylketonurics phenylalanine is present in quantity varying from 0.30 to 1 gm per 24 hours (12, 25, 39, 54, 92, 101), while the daily excretion in normal individuals averages 0.16 gm (36). In the blood from 10 to 50 mg per cent are found as compared with a range of 0.5-1.5 mg per cent in the normal (13, 39, 52, 93, 101). In the spinal fluid values of 6.1-8.3 mg per cent have been reported (12, 52), in sweat 8-10 mg per cent (54).

Phenylpyruvic acid may be easily isolated as its 2,4-dinitrophenylhydrazone (MP 187° C; C 52.3, H 3.49, N 16.28 per cent). The qualitative demonstration is simple: the addition of a few drops of ferric chloride solution to the acidified urine results in an intense green color. This reaction

can be applied to the quantitative determination of the keto acid in the urine (8, 87) and the blood (56) An alternative method extensively used but less specific since it measures the total keto acids, is based on the color reaction obtained by alkalizing the hydrazone of the acid (44)

In the urine of phenylketonurics phenylpyruvic acid is present in quantity varying from 0 3 to 2 gm per day (25, 32 38 51, 73 83 101) in the blood, from 0 2 to 1 4 mg per 100 ml of blood (56) No keto acids have been demonstrated in the spinal fluid In normal individuals no phenylpyruvic acid can be demonstrated either in urine or in blood with the available methods

Phenyllactic acid was isolated for the first time from the urine of a phenylketonuric by Zeller (103) and repeatedly determined in urine (9 25, 54, 101) Its values are below those for phenylpyruvic acid usually from 25 to 75 per cent lower It should be noted however that the quantitative methods used thus far are not entirely satisfactory since some phenylacetic acid is also determined in the test used

Phenylacetic acid was demonstrated for the first time in the urine by Woolf (102) It is present mostly conjugated with glutamine (10²) and partly with glucuronic acid (unpublished) in amounts similar to or lower than, phenylpyruvic acid Quantitative methods are not entirely satisfactory since some acid is lost during the process of extraction The acid is also present in the blood (unpublished)

Other metabolites The presence in the urine of phenylketonurics of an unidentified ether soluble keto acid which reduces Briggs reagent was reported by Berry and Woolf (8) A substance with a MP 200 222 giving an analysis C 63 14 H 4 60 N 14 03, was isolated by Dobriner et al (34) and a possibly similar nitrogen containing metabolite was demonstrated by Cowie (23) The presence of abnormally high amounts of p hydroxyphenyl lactic p hydroxyphenylacetic and o hydroxyphenylacetic acid has been reported (13)

It has been claimed (71 73) that abnormally high amounts of amino acids other than phenylalanine are present in the urine of phenylketonurics the condition being consequently classified in the group of amino aciduria together with Franconi s syndrome and Wilson s disease (73) However chromatographic analysis of amino acids in phenylketonuric urine using Moore and Stein s technique (76) showed that the only amino acid present in abnormal amounts is phenylalanine (94)

Feeding experiments

The effect of various diets upon the content of phenylalanine and its derivatives of the body fluids in phenylketonuria is of considerable sig

nificance Protein starvation reduces considerably the urinary output of phenylalanine and metabolites (51) Prolonged feeding of an adequate diet containing all indispensable amino acids but phenylalanine results in the disappearance of urinary phenylpyruvic acid and a reduction to normal of phenylalanine output (4 9) Diets rich in proteins increase the urinary excretion of phenylalanine and derivatives (51) Similar effects are noted in the blood content of both phenylalanine and phenylpyruvic acid (51 56)

Feeding DL-phenylalanine results in a considerable increase of urinary excretion (25 40 51 83) and increase of blood content (40 52) of phenylalanine and metabolites The D form appears to cause greater increase of urinary output than the L form (51) It should be noted that feeding of D or DL form (5 10 gm) to normal individuals produces slight ketonuria, while the same amount of the L form is completely metabolized by the normal organism When proteins are fed the higher the phenylalanine content of the protein the greater the output of phenylalanine and phenylpyruvic acid This can be easily observed by feeding equivalent (in N_2) amounts of gelatin (phenylalanine content 0 4–0 5 per cent) or casein (phenylalanine content 4 5 5 per cent) (51)

Feeding of phenylpyruvic acid to phenylketonurics *results in an increase* of urinary output (51 83) and blood content (56) of the keto acid some 50–75 per cent of which is excreted as such In normal individuals the percentage excreted after feeding is significantly less (56)

Feeding of phenyllactic acid has results similar to those of phenylpyruvic acid (51) Feeding of phenylglyceric phenylpropionic and phenylacetic acids causes no changes *in phenylalanine* or phenylpyruvic urinary output (51) No effect is noted following ingestion of tyrosine and its derivatives (p hydroxyphenylpyruvic dihydroxyphenylalanine homogentisic acid) or of other amino acids (51)

In order to complete the biochemical picture of the disease a few miscellaneous observations may be quoted

Serum brain liver and kidney proteins from phenylpyruvic subjects yield no difference from the normal in phenylalanine content (11) [illegible]

[illegible] s [illegible]

[illegible] have significance deserve confirmation Higher than normal values in the plasma globulins have been reported (61) Brain oxygen consumption is low (47)

It has been claimed that tests for hepatic functions show [illegible] values in [illegible]

The ob er[illegible]

can be applied to the quantitative determination of the keto acid in the urine (8, 87) and the blood (56). An alternative method extensively used but less specific since it measures the total keto acids is based on the color reaction obtained by alkalizing the hydrazone of the acid (44).

In the urine of phenylketonurics phenylpyruvic acid is present in quantity varying from 0.3 to 2 gm. per day (25, 32, 38, 51, 73, 83, 101), in the blood from 0.2 to 1.4 mg. per 100 ml. of blood (56). No keto acids have been demonstrated in the spinal fluid. In normal individuals no phenylpyruvic acid can be demonstrated either in urine or in blood with the available methods.

Phenyllactic acid was isolated for the first time from the urine of a phenylketonuric by Zeller (103) and repeatedly determined in urine (9, 25, 54, 101). Its values are below those for phenylpyruvic acid, usually from 25 to 75 per cent lower. It should be noted, however, that the quantitative methods used thus far are not entirely satisfactory since some phenyllactic acid is also determined in the test used.

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Other metabolites. The presence in the urine of phenylketonurics of an unidentified ether soluble keto acid which reduces Briggs' reagent was reported by Berry and Woolf (8). A substance with a MP 200-222° giving on analysis C 63.14, H 4.60, N 14.03 was isolated by Dobriner et al. (34) and a possibly similar nitrogen containing metabolite was demonstrated by Cowie (23). The presence of abnormally high amounts of p-hydroxyphenyllactic, p-hydroxyphenylacetic and o-hydroxyphenylacetic acid has been reported (13).

It has been claimed (71, 73) that abnormally high amounts of amino acids other than phenylalanine are present in the urine of phenylketonurics, the condition being consequently classified in the group of amino acidurias together with Fanconi's syndrome and Wilson's disease (73). However, chromatographic analysis of amino acids in phenylketonuric urine using Moore and Stein's technique (76) showed that the only amino acid present in abnormal amounts is phenylalanine (94).

Feeding experiments

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phenylketonuric urines of m hydroxyphenylacetic and m hydroxyphenyl lactic acid which are always present in normal urine would suggest that m hydroxylation is also defective in phenylketonuria (13)

The problem of the relationship if any of the metabolic error to the clinical symptomatology and in particular to the mental deficiency is still unsolved If one accepts the hypothesis of a causal relationship various possibilities present themselves for consideration

1 Phenylalanine deficiency The metabolism of phenylalanine an essential amino acid being impaired, defective structure of proteins, particularly brain protein may result Against this hypothesis is the finding of normal phenylalanine content of various tissues in phenylketonuria (11) The possibility remains however, that phenylalanine may not be available at some critical stage of development of the brain, for instance during myelinogenesis, thus explaining the myelin defect which has been described in the disease (5a) This possibility, to be sure is purely speculative no evidence of any type being available to support it

2 Secondary tyrosine deficiency Phenylalanine being a source of tyrosine in the normal in the phenylketonuric less tyrosine is available than in the normal Against this possibility is the finding of normal tyrosine value in the blood of patients and the fact that the addition to the diet of large amounts of tyrosine for as long as 6 months (23) produces no change in the clinical picture

3 Toxic action of phenylalanine and derivatives In favor of this possibility is the finding that experimentally in the growing rat the addition to the diet of phenylalanine (1a per cent) results in the death of the animal (unpublished) In one patient an adequate diet very low in phenylalanine, produced an appreciable improvement in the mental status and when phenylalanine was again given an immediate and dramatic deterioration was observed (9) A similar phenomenon was observed by Armstrong (4) These interesting observations deserve confirmation since the investigators themselves were unable to duplicate them

If this toxic hypothesis is confirmed the metabolite responsible for the toxic effect should be identified The finding that there is no correlation between phenylalanine phenylpyruvic and phenyllactic acid content and I Q (54 56) would suggest that these metabolites are not involved although in two cases mildly defective phenylketonurics were found to excrete very little phenylpyruvic acid (22 41) Phenylacetic acid has been incriminated by Woolf (101) and p hydroxyphenyl and o hydroxyphenyl compounds by Boscott and Bickel (13) but the data are too scanty to justify any definite conclusions

The distinct possibility finally should be stressed that the relationship of the metabolic error to the clinical symptomatology is not a causal one

tion Sedimentation rate has been reported to be increased (71), an observation not confirmed in 20 personal cases Increased creatine output has been described (89)

The problem of *the biochemical nature of phenylketonuria* has been the object of considerable investigation Several hypotheses have been advanced

1 The error consists of a block in the metabolism of phenylalanine at the stage of phenylpyruvic acid (83), the unmetabolized acid would then be excreted in the urine The presence of large amounts of phenylalanine in the blood, the ability of the patients to aminate the keto acid (52) and the generally accepted fact that phenylpyruvic acid is not a normal metabolite of phenylalanine make this hypothesis improbable

2 The error consists of an abnormal racemization of phenylalanine, the naturally occurring L form being converted by the phenylketonuric organism into the D form which is subsequently deaminated in the kidneys and excreted as phenylpyruvic acid (41) The finding in the body fluids of patients of only the L and never the D form of phenylalanine (41 88) seems difficult to reconcile with this hypothesis although there remains the possibility that deamination occurs at a very fast rate, preventing the accumulation of measurable amounts of D phenylalanine

3 The error consists of a blockage in the conversion of phenylalanine into tyrosine the unmetabolized amino acid would then accumulate in the body fluid and be excreted as such or as its deaminated products phenylpyruvic phenyllactic and phenylacetic acid (53)

The following findings seem to support this hypothesis In normal individuals, but not in phenylketonurics the ingestion of phenylalanine is followed by a temporary increase in the blood of tyrosine reacting substance (53) In normal individuals but not in phenylketonurics feeding of isotopic phenylalanine results in the presence of considerable amounts of labeled tyrosine in the blood proteins (99) In the normal but not in the phenylketonuric liver an enzyme system is present which catalyzes the conversion of phenylalanine into tyrosine (57)

[illegible]

very partial conversion of phenylalanine into tyrosine may be explained by the presence of a still unknown alternative metabolic pathway It is possible also that in the phenylketonuric defective enzymatic system inhibitors are present or cofactors absent (99)

It is tempting to consider this characteristic failure of parahydroxylation as strictly specific for phenylalanine in fact antipyrine is normally parahydroxylated by the phenylketonuric (99) However the absence in

(93) In the Bernstein method s is the number of children per sibship, n, the number of s member sibships, t, the number of affected children in s member sibships, x, the theoretical expectation of affected children in each s member sibship which is given by the formula $\frac{sp}{1 - q^s}$, where p is assumed a priori to be 0 25 on the recessive hypothesis and $q = 1 - p$ The quadratic error m^2 is $x_s(q - sxq^s)$ In the Weinberg method, n', is the number of s member sibships having 'probands', t, their number of affected children y, is the theoretical expectation given by the formula $\frac{sp\,1 - (1 - r)(1 - rp)^{s-1}}{1 - (1 - rp)^s}$ where r represents the 'ascertainment rate' and is expressed by the ratio of $\frac{\Sigma p(p - 1)}{p(t - 1)}$ as given in table 4 In the Lenz method n'', is the reduced number of s member sibships obtained by adding for each family the ratio of 'probands' to affected children, p is the number of probands in the s member sibships

It may be seen that in both Weinberg and Lenz methods, the difference between expectation and observation is well within the standard error For the method of Bernstein which is correctly applied only when the material is collected at random and not as in the present case, with a certain choice the difference is three times the standard error

It appears in conclusion that the application of adequate statistical methods indicates a ratio of affected to normal children compatible with the hypothesis of a single recessive autosomal gene

Mating of affected individuals

Because of the very nature of the disease, it is not likely that many phenylketonurics will have offspring There are in fact, only 5 instances of mating of phenylketonurics In three personal cases the four offspring were normal thus conforming to expectation on the hypothe[illegible] ingle

the

ence

two

[illegible] a high grade phenylketonuric woman

In two other families the mating of an affected with an apparently normal individual resulted in two normal and two affected (50), and one normal and one affected offspring (18) *On the hypothesis of a single recessive gene* these cases can be explained only on the hardly acceptable assumption that in either family the apparently *normal* parent was heterozygous There remains the possibility that in these families a mode of inheritance other than recessive was present

No record exists of the mating of two affected individuals

The two phenomena, biochemical and mental defect, may be the expression of a genic action, pleiotropic in nature. The role of the gene in the determination of the biochemical error is seen in the genic activity of synthesis of the particular enzyme catalyzing the conversion of phenylalanine into tyrosine. It is known, in fact, that the field of action of the gene may be restricted to a single chemical step in the metabolism of an amino acid (48). The role of the gene in the determination of mental defect is not clear but other examples of genetically determined types of mental retardation are known.

GENETIC ASPECTS

Superficial examination of the clinical data clearly shows that phenylketonuria is often a familial disease. Out of 266 sibships in which sufficient data are available, 46 per cent have two or more affected sibs. If the sibships with only one member are excluded, the figure rises to 53 per cent. The crude ratio of affected to normal sibs in the total sibships is 6[illegible]

In large series of patients (41, 50, 78) analysis of data has indicated that environmental agencies play no significant role in the causation of phenylketonuria and that the condition is caused by a single autosomal recessive gene. The genetic study is facilitated by the fact that (1) the identification of the condition is simple and exact, being made by a chemical test; (2) the character segregates sharply, affected individuals being entirely different biochemically from non-affected ones; (3) the disease fulfills the requirement of being a unity in a biological (biochemical) sense.

It seems of interest to analyze all data available thus far in the light of this hypothesis by taking into consideration (1) the corrected ratio of affected to normal children in the sibship, (2) the rate of parental consanguinity, (3) the distribution of the condition among collateral relatives.

1. *Ratio of affected to normal children.* When both parents are normal (heterozygous), as in almost all the cases of phenylketonuria, the theoretical percentage of affected children is 25 per cent on the hypothesis of a single autosomal recessive gene. *In table 20 the results are given of Weinberg's* sib and proband methods (93) as applied to phenylketonuric families. *s* is the number of sibs in the family, *t* the number of affected sibs, *p* the number of primary cases (proband) from which the investigation of the family started (i.e., cases usually observed in institutions or hospitals). It may be seen that the percentage according to the sib method is 27.37, the difference between observed value and theoretical expectation being within the standard error. The percentage according to the proband method is 22.38, the difference again being within the standard error. The latter method is more appropriate to the type of family material presented.

In table 21 the material is arranged according to three a priori methods

TABLE 20—*Continued*

Family	s	t	t(s − 1)	t(t − 1)	p	p(s − 1)	p(t − 1)	Family	s	t	t(s − 1)	t(t − 1)	p	p(s − 1)	p(t − 1)
84	4	1	3	0	1	3	0	125	3	2	4	2	2	4	2
85	8	2	14	2	2	14	2	126	2	1	1	0	1	1	0
86	5	1	4	0	1	4	0	127	4	1	3	0	1	3	0
87	6	2	10	2	1	5	1	128	2	2	2	2	1	1	1
88	5	2	8	2	2	8	2	129	2	1	1	0	1	1	0
89	5	3	12	6	1	4	2	130	4	1	3	0	1	3	0
90	4	2	6	2	2	6	2	131	3	2	4	2	2	4	2
91	4	1	3	0	1	3	0	132	5	1	4	0	1	4	0
92	3	1	2	0	1	2	0	133	2	1	1	0	1	1	0
93	4	2	6	2	2	6	2	134	3	2	4	2	1	2	0
94	6	2	10	2	1	5	1	135	1	1	0	0	1	0	0
94a	4	1	3	0	1	3	0	136	2	2	2	2	1	1	1
95	1	1	0	0	1	0	0	137	4	1	3	0	1	3	0
96	1	1	0	0	1	0	0	138	1	1	0	0	1	0	0
97	3	3	6	6	1	2	2	139	3	2	4	2	1	2	0
98	3	1	2	0	1	2	0	140	1	1	0	0	1	0	0
99	3	1	2	0	1	2	0	141	1	1	0	0	1	0	0
100	6	2	10	2	2	10	2	142	3	2	4	2	1	2	0
101	3	1	2	0	1	2	0	143	2	1	1	0	1	2	0
102	2	1	1	0	1	1	0	144	2	1	1	0	1	1	0
103	4	2	6	2	2	6	2	145	4	2	6	2	1	3	1
104	4	1	3	0	1	3	0	146	1	1	0	0	1	0	0
105	1	1	0	0	1	0	0	147	8	2	14	2	1	7	1
106	4	1	3	0	1	3	0	148	6	2	10	2	1	5	1
107	3	2	4	2	2	4	2	148a	5	2	8	2	1	4	1
108	7	2	12	2	2	12	2	149	8	3	21	6	1	7	2
109	2	2	2	2	1	1	1	150	5	3	12	6	1	4	2
110	2	1	1	0	1	1	0	151	7	1	6	0	1	6	0
111	1	1	0	0	1	0	0	152	5	1	4	0	1	4	0
112	5	1	4	0	1	4	0	153	2	1	1	0	1	1	0
113	1	1	0	0	1	0	0	154	1	1	0	0	1	0	0
114	4	3	9	6	2	6	4	155	3	1	2	0	1	2	0
115	5	2	8	2	2	8	2	156	6	2	10	2	1	5	1
116	2	1	1	0	1	1	0	157	5	2	8	2	1	4	1
117	4	1	3	0	1	3	0	158	3	1	2	0	1	2	0
118	4	2	6	2	1	3	1	159	2	1	1	0	1	1	0
119	5	1	4	0	1	4	0	160	6	2	10	2	1	5	1
120	4	2	6	2	2	6	2	161	1	1	0	0	1	0	0
121	3	1	2	0	1	2	0	162	5	1	4	0	1	4	0
122	1	1	0	0	1	0	0	163	4	1	3	0	1	3	0
123	3	2	4	2	1	2	1	164	13	4	48	12	1	12	3
124	2	1	1	0	1	1	0	165	4	3	9	6	1	3	2

TABLE 20

Weinberg's "Sib Methods"

Family	s	t	t(s − 1)	t(t − 1)	p	p(s − 1)	p(t − 1)	Family	s	t	t(s − 1)	t(t − 1)	p	p(s − 1)	p(t − 1)
1	7	2	12	2	2	12	2	42	4	2	6	2	1	3	1
2	3	1	2	0	1	2	0	43	3	2	4	2	2	4	2
3	4	1	3	0	1	3	0	44	2	1	1	0	1	1	0
4	2	2	2	2	1	1	1	45	5	2	8	2	1	4	1
5	1	1	0	0	1	0	0	46	3	1	2	0	1	2	0
6	3	1	2	0	1	2	0	47	1	1	0	0	1	0	0
7	1	1	0	0	1	0	0	48	3	3	6	6	2	4	4
8	2	1	1	0	1	0	0	49	4	3	9	6	2	6	4
9	8	2	14	2	1	7	1	50	6	2	10	2	1	5	1
10	2	2	2	2	1	1	1	51	5	2	8	2	1	4	1
11	7	2	12	2	2	12	2	52	3	1	2	0	1	2	0
12	7	4	24	12	3	18	9	53	1	1	0	0	1	0	0
13	5	3	12	6	1	4	2	54	6	4	20	12	3	15	9
14	2	1	1	0	0	0	0	55	4	1	3	0	1	3	0
15	2	1	1	0	1	1	0	56	3	1	2	0	1	2	0
16	2	1	1	0	1	1	0	57	2	1	1	0	1	1	0
17	3	1	2	0	1	2	0	58	4	1	3	0	1	3	0
18	1	1	0	0	1	0	0	59	2	1	1	0	1	1	0
19	2	1	1	0	1	1	0	60	2	1	1	0	1	1	0
20	3	1	2	0	1	2	0	61	7	2	12	2	1	6	1
21	10	5	45	20	1	9	4	62	1	1	0	0	1	0	0
22	4	1	3	0	1	3	0	63	2	1	1	0	1	1	0
23	4	1	3	0	1	3	0	64	3	2	4	2	1	2	1
24	5	3	12	6	3	12	6	65	1	1	0	0	1	0	0
25	2	1	1	0	1	1	0	66	9	2	16	2	2	16	2
26	2	1	1	0	1	1	0	67	4	2	6	2	2	6	2
27	6	2	10	2	2	10	2	68	1	1	0	0	1	0	0
28	3	1	2	0	1	2	0	69	2	1	1	0	1	1	0
29	3	1	2	0	1	2	0	70	3	1	2	0	1	2	0
30	5	1	4	0	1	4	0	71	6	2	10	2	1	5	1
31	2	1	1	0	1	1	0	72	4	1	3	0	1	3	0
32	6	1	5	0	1	5	0	73	3	1	2	0	1	2	0
33	4	1	3	0	1	3	0	74	3	1	2	0	1	2	0
34	12	4	44	12	1	11	3	75	3	1	2	0	1	2	0
35	6	2	10	2	2	10	2	76	2	1	1	0	1	1	0
35a	8	2	14	2	1	7	1	77	3	2	4	2	1	2	1
36	4	2	6	2	1	3	1	78	3	1	2	0	1	2	0
37	5	1	4	0	1	4	0	79	3	2	4	2	2	4	2
38	6	3	15	6	3	15	6	80	4	1	3	0	1	3	0
39	3	2	4	2	1	2	1	81	5	3	12	6	1	4	2
40	4	1	3	0	1	3	0	82	1	1	0	0	1	0	0
41	4	1	3	0	1	3	0	83	2	2	2	2	1	1	1

TABLE 20—*Concluded*

Family	s	t	t(s − 1)	t(t − 1)	p	p(s − 1)	p(t − 1)	Family	s	t	t(s − 1)	t(t − 1)	p	p(s − 1)	p(t − 1)
250	3	2	4	2	1	2	1	259	4	3	9	6	1	3	2
251	2	1	1	0	1	1	0	260	3	3	6	6	2	—	—
252	5	2	8	2	2	8	2	261	11	2	20	2	2	20	2
253	1	1	0	0	1	0	0	262	2	1	1	0	1	1	0
254	2	1	1	0	1	1	0	263	4	2	6	2	2	—	—
255	2	1	1	0	1	1	0	264	12	5	55	20	2	22	8
256	2	2	2	2	2	2	2	265	2	2	2	2	1	1	0
257	1	1	0	0	1	0	0	266	3	1	2	0	1	2	0
258	5	1	4	0	1	4	0	Total	1094	433	1571	430	312	992	222

Sib method

$$P = 100 \frac{\Sigma t(t-1)}{\Sigma t(s-1)} = 100 \frac{430}{1571} = 27.37 \pm 2.57$$

Proband method

$$P = 100 \frac{\Sigma p(t-1)}{\Sigma p(s-1)} = 100 \frac{222}{992} = 22.38 \pm 2.66$$

Families 1 to 146 are from personal observation 147 to 192 are from Munro (78) 193 to 214 from Følling et al (41) The other families are from the following references 215 to 222 (43) 223 to 229 (63) 230 to 233 (92) 234 to 237 (16) 238 239 (60) 240 241 (74) 242 to 245 (71) 246 to 248 (101) 249 250 (13) 251 (29) 252 (30) 253 (31) 254 (18) 255 (21) 256 (100) 257 (61) 258 (60) 259 (19) 260 (67) 261 (20) 262 (5), 263 (73), 264 (85), 265 (69) 266 (9)

2 *Rate of consanguinity* Consanguinity among parents was found in 8 of the 146 families personally observed (5 5 per cent), in 5 of the 47 families described by Munro (10 per cent) (78) and in 4 of Følling s (41) 23 sibships (17 per cent) The percentage of these combined data is 8.33 Other isolated instances of consanguinity have been reported (27, 60 74) It is well known that the ratio of the frequency of a condition in offspring of consanguineous marriage to its frequency in offspring of unrelated marriages is high in rare recessive conditions Using Lenz formula (93), $\frac{a}{a + 16p}$ where a is the incidence of cousin marriage in the general population (about 1 per cent), and p the gene frequency of phenylketonuria or the square root of the incidence of the condition in the general population 0 004 per cent (see page 261) the expected incidence of consanguineous marriages is 7 per cent, which is close to the observed incidence 8 per cent

3 *Distribution of the condition among relatives other than sibs* Data on half sibs are available for 65 individuals (41, 50 78) 63 were normal as theoretically expected The two exceptions occurred in one family where

TABLE 20—*Continued*

Family	s	t	t(s − 1)	t(t − 1)	p	p(s − 1)	p(t − 1)	Family	s	t	t(s − 1)	t(t − 1)	p	p(s − 1)	p(t − 1)
166	4	1	3	0	1	3	0	208	6	2	10	2	1	5	1
167	4	1	3	0	1	3	0	209	3	1	2	0	1	2	0
168	6	2	10	2	1	5	1	210	3	2	4	2	2	4	2
169	2	2	2	2	1	1	1	211	10	2	18	2	2	18	2
170	1	1	0	0	1	0	0	212	2	2	2	2	2	2	2
171	1	1	0	0	1	0	0	213	10	4	36	12	2	18	6
172	10	2	18	2	1	9	1	214	6	1	5	0	1	5	0
173	2	1	1	0	1	1	0	215	8	3	21	6	3	21	6
174	1	1	0	0	1	0	0	216	3	1	2	0	1	2	0
175	2	1	1	0	1	1	0	217	4	1	3	0	1	3	0
176	11	2	20	2	1	10	1	218	5	2	8	2	1	4	1
177	5	1	4	0	1	4	0	219	3	1	2	0	1	2	0
178	5	3	12	6	1	4	2	220	1	1	0	0	1	0	0
179	3	2	4	2	1	2	1	221	4	2	6	2	1	3	1
180	3	2	4	2	1	2	1	222	2	1	1	0	1	1	0
181	3	2	4	2	1	2	1	223	2	1	1	0	1	1	0
182	9	2	16	2	1	8	1	224	4	1	3	0	1	3	0
183	3	2	4	2	1	2	1	225	3	1	2	0	1	2	0
184	1	1	0	0	1	0	0	226	1	1	0	0	1	0	0
185	12	3	33	6	1	11	2	227	7	2	12	2	1	6	1
186	7	3	18	6	1	6	2	228	4	2	6	2	1	3	1
187	8	3	21	6	1	7	2	229	6	2	10	2	1	5	1
188	2	1	1	0	1	1	0	230	1	1	0	0	1	0	0
189	10	3	27	6	1	9	2	231	2	1	1	0	1	1	0
190	4	2	6	2	1	3	1	232	1	1	0	0	1	0	0
191	2	1	1	0	1	1	0	233	4	1	3	0	1	3	0
192	6	4	20	12	1	5	3	234	5	1	4	0	1	4	0
193	2	2	2	2	2	2	2	235	1	1	0	0	1	0	0
194	2	2	2	2	1	1	1	236	4	2	6	2	2	3	4
195	6	2	10	2	2	10	2	237	2	1	1	0	1	1	0
196	6	1	5	0	1	5	0	238	3	3	6	6	1	2	0
197	9	2	16	2	2	16	2	239	2	2	2	2	1	1	0
198	7	1	6	0	1	6	0	240	4	1	3	0	1	3	0
199	7	3	18	6	1	6	2	241	8	2	14	2	1	7	1
200	6	2	10	2	2	10	2	242	3	1	2	0	1	2	0
201	5	1	4	0	1	4	0	243	2	1	1	0	1	1	0
202	2	1	1	0	1	1	0	244	4	2	6	2	1	3	1
203	5	2	8	2	2	8	2	245	1	1	0	0	1	0	0
204	6	2	10	2	1	5	1	246	2	2	2	2	?	—	—
205	3	1	2	0	1	2	0	247	5	2	8	2	?	—	—
206	9	3	24	6	2	16	4	248	3	2	4	2	1	2	1
207	11	1	10	0	1	10	0	249	2	2	2	2	1	1	1

TREATMENT

In view of the fact that several vitamins are of significance in the intermediary metabolism of amino acids, thiamine (50 mg/day), nicotinic acid (500 mg/day), pyridoxine (5 mg/day), citrovorum factor (3 mg/day), ascorbic acid (100 mg/day) were administered for one week or longer to patients kept on nitrogen constant diet. No change was observed in the output of phenylderivatives (unpublished).

Glutamic acid was used with marked improvement of mental performances by some investigators (31, 68, 71). These results have not been confirmed (101). Personal observation of patients who were given high doses of glutamic acid for several months was likewise negative. Adrenocorticotropic hormone and cortisone administration produced increase of phenylderivatives output for a few days but no improvement in mental condition (unpublished).

The extraordinary results of feeding a diet very low in phenylalanine (4, 9) have already been mentioned (page 266). Remarkable is the case of a patient (9) who showed relapse in his mental status whenever the diet was supplemented with phenylalanine. Transfusion of a patient with large amounts of blood from a normal donor was attempted in one case (30, 31) without demonstrable results on the metabolic error.

The demonstration that the enzyme system which catalyzes the conversion of phenylalanine into tyrosine is defective in phenylketonuria (57) makes it possible in the future to attempt a treatment of the metabolic error, if not of the mental defect, with enzyme preparations.

Although the disease is clearly genetic in nature, preventive measures are limited in scope. Sterilization of affected individuals appears hardly justified in the majority of cases since procreation is sharply limited by the intellectual condition of the patients. Sterilization of the heterozygotes, theoretically justifiable if detection of the carrier status could be possible, would involve the staggering figure of 1 per cent of the general population (86). There is sufficient ground, however, *to discourage* parents of phenylketonurics from having other children and to advise members of phenylketonuric families against consanguineous marriages.

DISCUSSION

DR. P

of that sort

DR. C. NASH HERNDON (Winston-Salem, N. C.): The careful and detailed investigations

TABLE 21

A priori methods

s	Bernstein				Weinberg				Lenz			
	n_s	t_s	$x_s n_s$	$m^2_x n_s$	n'_s	t'_s	$y_s n'_s$	$m^2_y n'_s$	n''_s	p	$z_s n''_s$	$m^2_z n''_s$
1	34	34	34 00	0 00	34	34	34 00	0 00	34 00	34	34 00	0 00
2	55	70	62 86	6 71	54	68	65 12	6 69	48 50	57	55 48	5 92
3	51	78	66 15	13 41	50	75	70 65	8 50	42 33	56	54 90	11 13
4	45	68	65 83	18 90	44	66	69 16	9 63	38 00	52	55 59	15 96
5	28	50	45 89	16 57	27	48	49 49	8 10	21 16	33	34 68	12 59
6	22	45	40 15	17 07	22	45	45 64	6 60	15 50	31	28 29	12 03
7	10	22	20 20	9 70	10	22	22 61	3 94	8 42	15	17 01	8 17
8	8	19	17 78	9 38	8	19	19 81	3 75	4 66	11	10 36	5 46
9	4	9	9 73	5 52	4	9	10 78	2 00	3 16	7	7 69	4 36
10	5	16	13 24	7 96	5	16	14 55	2 75	2 41	7	6 38	5 84
11	3	5	8 61	5 41	3	5	9 41	1 77	2 50	4	7 18	4 51
12	3	12	9 29	4 06	3	12	10 08	1 80	0 92	4	2 85	1 86
13	1	4	3 33	2 33	1	4	3 58	0 71	0 25	1	0 83	0 57
	—	432	397 06	117 02	—	423	424 68	56 26	—	312	315 19	88 33

Bernstein method	Difference (432–397 06)	34 94	Standard error 10 8
Weinberg method	Difference (423–424 68)	1 68	Standard error 7 5
Lenz method	Difference (312–315 19)	3 19	Standard error 9 4

the father had married two sisters, both matings resulting in some affected children. A study of the incidence of the disease among cousins of affected children would be of interest, but complete data are available only in a limited number of cases (10, 50, 78). There were 2 affected cousins in the personally observed material, and 2 in 571 cousins examined by Munro (78). These figures conform to expectation on the recessive hypothesis, the theoretical percentage being of the order of 0 3, assuming the incidence of the disease is 0 004 per cent.

Linkage

Although the material provided by cases of phenylketonuria is particularly suitable for investigation of possible linkages, no conclusive evidence has been obtained in this field. Data suggesting linkage between the disease and the ABO agglutinogens have been published (23, 78, 85) but this linkage, if present, is not close enough to permit identifying the heterozygous state of the condition.

It has been suggested that the heterozygote for phenylketonuria shows a tendency to become psychotic (82) but data on large series of families have failed to confirm this interesting hypothesis (50, 78).

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that Dr Jervis has summarized concerning the genetics and biochemistry of phenylketonuria may well serve as a model for work in this field The whole story of phenylketonuria from the first recognition of the metabolic defect as a clinical entity to the pinpointing of the defect to the absence of a specific enzyme responsible for conversion of phenylalanine into tyrosine is a very significant one Several years ago Penrose pointed out that no single gene identified as being responsible for any variety of mental deficiency accounts for as much as 1 per cent of the total load of mental defect in our population It seems likely that there should be a number of other specific syndromes still concealed in the large residual group of undifferentiated mental defect Certainly the treatment of mental retardation is one of the discouraging aspects of therapeutics Hope for improvement in this field lies in work such as Dr Jervis has presented, aimed at discovering the specific abnormality underlying the condition The newer biochemical techniques that have been developed recently, including the use of radioactive isotopes and analysis by paper chromatography, may well offer new tools for combined genetic and biochemical attack on other problems in this group The investigations that Dr Jervis has described in connection with phenylketonuria should not be looked upon as a unique situation applying only to a small fraction of mentally retarded patients, but as a model of what might well be accomplished by applying these and other appropriate techniques to other problems that now remain obscure

Dr C Glen King (New York N Y) I would like to ask a question—whether there is any evidence that phenylalanine tolerance tests might become a means of detecting the carriers prenatally It would seem to be quite an important development in terms of the management of these individuals if such a test could be controlled

President Hooker We have a question from the floor from Dr Mark Zeifert of Fresno California "Please discuss the effect of jaundice on the urine test"

Dr George A Jervis (Closing) Concerning the feeding of a low phenylalanine diet the first experiment was done by Bickel in England A dramatic improvement in behavior was noted in a little girl one year of age When phenylalanine was again added to the diet the behavior changed again dramatically Dr Bickel wrote me that he was not able to confirm these results in another patient Dr Armstrong in Salt Lake City obtained similar results in a young child who was fed this diet over a period of six months We have started similar experiments but so far we have not seen much result as far as I Q changes are concerned In any event it is certainly very interesting that for the first time one can influence remarkably the behavior of a patient by changing his diet

With regard to the fact that most phenylketonurics are of the blonde type it is well known that there is a very close relationship between pigment formation and tyrosine metabolism However in phenylketonuria I would be inclined to think there is no connection between metabolic abnormality and lack of pigment It would be difficult in fact to explain the occasional presence of phenylketonuria in individuals with dark skin

Concerning the very important question asked by Dr King about the possibility of detecting the heterozygote this would be of course a fundamental piece of research in phenylketonuria Thus far, no biochemical difference has been found between heterozygous or normal individuals

Concerning the question of jaundice ferric chloride may give a green color in icteric urine Other biochemical tests are necessary in such cases and the hydrazone of phenylpyruvic acid should be identified The green chloride test is very useful for screening purposes

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CHAPTER XVII

THE INHERITANCE OF NEUROMUSCULAR DISEASE

FRANK H TYLER

The more common hereditary disorders which involve the neuromuscular apparatus can be divided for convenience into the muscular dystrophies and the neural atrophies In addition to these disorders affecting the muscle cells and the nerve tissues respectively there are certain functional abnormalities which affect the neuromuscular system such as periodic paralysis

In this report studies of the inheritance of neuromuscular disease in the Laboratory for the Study of Hereditary and Metabolic Disorders will be summarized In most instances our approach has been the careful study of *all* available members of a pedigree in which a given trait is *known to occur* By analysis of these data the pattern of inheritance of several of these disorders has become quite clear In addition a more accurate picture of the clinical characteristics of the disorders has been obtained because it has been possible to make a wide random sampling of the clinical manifestations of the genetic trait This clinical information is also of great aid in identifying the minimally affected and in excluding from the presumably affected group subjects who have other types of neuromuscular disease Lack of accurate primary data frequently has led to confusion in the older literature on this subject

Among the several hundred patients with muscular dystrophy whom we have observed all but six have the characteristics of one of three relatively common syndromes facioscapulohumeral, childhood or myotonic dystrophy (1)

Some years ago we presented a large pedigree in which many cases of facioscapulohumeral dystrophy (figs 47 and 48) were found (2) The dominant character of the inheritance in this pedigree is evident, it is confirmed by the analysis of the children of the back-cross matings in table 22 This trait is easily recognizable in adolescent patients or in older persons but is extremely variable in its severity As indicated in table 22 the penetrance appears to be complete We have now observed three additional pedigrees in which facioscapulohumeral dystrophy is present in

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TABLE 23

Normal and dystrophic children of back cross matings in facioscapulohumeral progressive muscular dystrophy

Phenotype	Observed	Calculated
Normal (dd)	143	136 5
Dystrophic (Dd)	130	136 5

a similar number of patients In each the pattern of inheritance is equally clearly dominant We have also observed the trait in 13 additional pedigrees of which a smaller group of people could be examined However, in each the data are consistent with even though not extensive enough to prove a dominant pattern of inheritance Although we have not demonstrated indubitable examples of new mutation of this trait they will undoubtedly appear However in the light of the benign character of the trait and the nearly normal reproductiveness of the affected members only rare mutants are required to maintain the present high population incidence of this disorder

Childhood progressive muscular dystrophy has been observed in a larger number of pedigrees (3) but in fewer total patients than the previous disorder Many of these pedigrees (fig 49) show the disorder in multiple male children of a female line Such a pattern suggests sex linked recessive inheritance Analysis of the pedigrees in which multiple cases have occurred (table 23) shows that half of the male children of the female line are dystrophic Such data leave little doubt of the sex linked recessive character of the trait

In a number of additional pedigrees however single cases or, in one example a pair of identical twins had this disease The number of normal male offspring (nine or more) of the female line was such as to make it highly improbable that the recessive trait had been transmitted for many generations in the female line (fig 50) Of the possible explanations

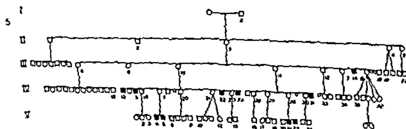


Fig 49 Pedigree of [...] (From Proceedings of t[...] America 1951 by perm[...]

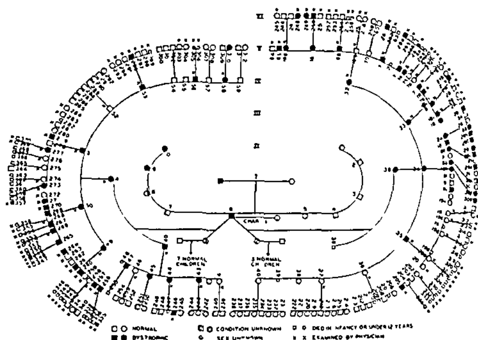


Fig 47

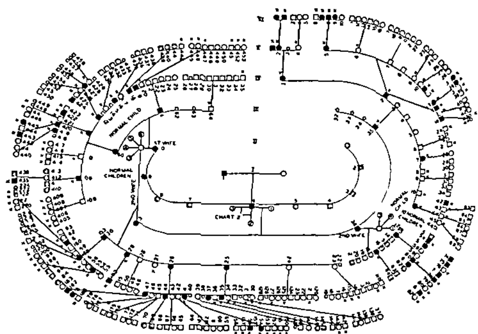


Fig 48

Figs 47 and 48 An extensive pedigree in which facioscapulohumeral dystrophy occurs as a typical dominant trait (From "Proceedings of the First Medical Conference", Muscular Dystrophy Associations of America, 1951, by permission)

TABLE 94

Mutation rate of childhood progressive muscular dystrophy

$$\frac{6\ (\text{Isolated Patients born in Utah 1931–1940}) \times 3}{183\,000\ (\text{X Chromosomes in Utah 1931–1940})} = 9.5 \times 10^{-5}$$

Mutation Rate = $\frac{1}{3}$ (1 − fertility) Frequency of trait in Males

$$= \frac{1}{3}\,(1 - 0) = \frac{18\ (\text{Total Patients born in Utah 1931–1940})}{63\,000\ (\text{Total Males born in Utah 1931–1940})}$$

$$= 9.5 \times 10^{-5}$$

The third common type of muscular dystrophy, myotonic dystrophy, has been observed in 18 pedigrees. Two of these are illustrated in figure 51. Again we see that the trait passes from generation to generation directly and without regard to sex. The inheritance in the pedigrees which we have observed is typical of a somatic dominant trait. However, these pedigrees tend to be much shorter than those observed in *facioscapulohumeral* dystrophy. The reduced effective fertility of these patients is probably responsible. It results in part from the severe disability present at an early age in some patients and in part from the gonadal disease which is a part of the trait. Like facioscapulohumeral dystrophy this is an extremely variable trait with some affected members showing only minimal manifestations. Again the most careful and detailed clinical examination of patients is required to identify the minimally affected patients and to exclude those with other diseases.

One problem which has been the subject of considerable argument recently is the question of the identity of myotonia congenita with myotonia dystrophica (7). It is unquestionably true that most patients with myotonia also have dystrophic features. In addition, patients are occasionally observed in pedigrees of myotonic dystrophy in whom myotonia is the only apparent anomaly. On the other hand, pedigrees have been reported in which none of a sizeable group had any dystrophic

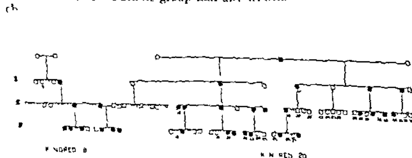


Fig. 51. Dominant inheritance of myotonic dystrophy in two pedigrees

TABLE 23

Childhood progressive muscular dystrophy

	Number of kindreds	Individuals in direct line from first female		
		Females (abnormal)	Males (normal)	Males (affected)
Multiple patients in each pedigree	5	6[illegible]	[illegible]7	[illegible]
Isolated patients	1[illegible]	110	110	13

that can be proposed for these apparently isolated cases the occurrence of new mutations seems most reasonable and calculation of the data by two techniques (table 24) yields the same value of 9.5×10^{-5} of the frequency of mutations (4). It must be recognized however that the same clinical manifestations might be determined in these patients by some completely independent genetic mechanism or by some non genetic factor.

The clinical recognition of childhood dystrophy is relatively simple. It has usually been called pseudohypertrophic progressive muscular dystrophy but many patients with facioscapulohumeral dystrophy and a few with myotonic dystrophy as well as patients with certain other diseases also have pseudohypertrophy of muscle (5). Our term childhood also has obvious objections e.g. we have recognized patients with facioscapulohumeral dystrophy as early as age seven and severe manifestations of the childhood variety may not appear until adolescence. However it does avoid the confusion caused by such terms as Duchenne which have been used in the literature in referring to many different traits and the clumsy and no more satisfactory terms which have been proposed by others (6).

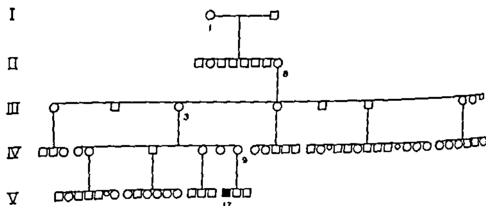


Fig 50 A typical example of childhood dystrophy in a pedigree with many other normal male children of the female line. (From Proceedings of the First Medical Conference Muscular Dystrophy Associations of America 1951. By permission)

dominant inheritance However, they have depended on the family histories as recorded in routine hospital charts In spite of the undoubted excellence of the hospitals concerned we believe that such data concerning the inheritance of human traits are unreliable

We have observed a small number of patients without a history of involvement of other members of the family who have the clinical and pathologic manifestations of progressive muscular dystrophy and who differ from the three groups described The group is heterogeneous The small number of patients makes speculation about their possible genetic mechanisms unproductive

It is our experience that most patients who on superficial examination appear to have progressive muscular dystrophy and yet do not fit any of the common types on more careful study prove to have a different disease (1) We have most frequently found this differential diagnosis difficult in patients with polymyositis or infantile muscular atrophy

Two types of hereditary neural atrophy are relatively common These are peroneal muscular atrophy and infantile muscular atrophy Many patients with peroneal muscular atrophy also have signs of long tract involvement in the spinal cord A variety of combinations of lesions has been observed Clinical findings suggestive of corticospinal extrapyramidal posterior column cerebellar and basal ganglion lesions have been observed in various combinations together with the distal atrophy and sensory changes characteristic of peroneal atrophy The variability within a pedigree is considerably less than that observed between pedigrees It would appear that each is the effect of different mutation or of multiple ver closely '

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Infantile muscular atrophy is an extremely variable disease which ranges from the rapidly fatal disease of infancy described by Oppenheim to the more slowly progressive neural atrophy beginning in childhood Some of the patients stabilize at greater or lesser levels of disability and survive to adult life We have observed only a small number of affected children in each of the pedigrees in which we have observed this trait The data are quite similar to those reported by Brandt (10) and like his show an excess of involved females and a higher number of affected siblings than would be expected for a simple recessive trait Because of the limited data however a final conclusion concerning the nature of the inheritance is impossible at present

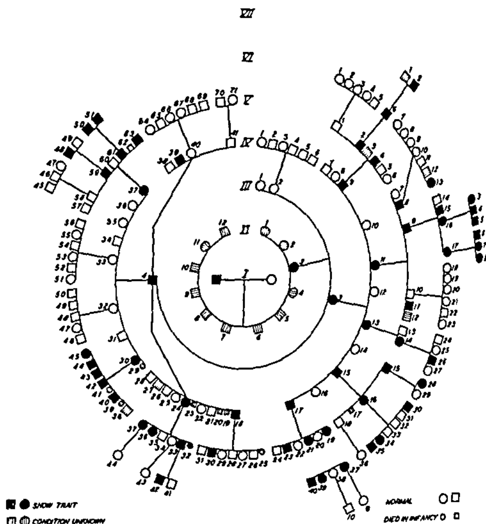


Fig 52 Extensive occurrence of paramyotonia in a pedigree

tonia (fig 52) Thus it seems probable that rare genetically distinct examples of myotonia congenita and paramyotonia do occur but their clinical differentiation from the more common myotonic dystrophy can only be accomplished with certainty by careful examination of a considerable number of patients all of whom derive their trait from a common source

As one reviews the literature and reclassifies the published pedigrees of progressive muscular dystrophy in which a considerable number of patients have been carefully examined, one finds that nearly all fit this simple classification and the inheritance is consistent with the patterns which we have observed Julia Bell (8) and Madelaine Brown (9) have published reports which deny that dominant inheritance occurs commonly in muscular dystrophy In each of these series a large and excellent hospital experience has been reviewed without the discovery of an example of apparent

congenita but in which certain individuals eventually developed characteristic myopathic changes such as are seen in the fully developed cases of dystrophia myotonica. So we feel that these two diseases are variants of the same disease process. The same is almost certainly true of paramyotonia since all cases of myotonia are made worse by cold and the fact that some show myotonia only when cold, is not I think a necessary reason for classifying them as a separate entity. However we would agree with Dr Tyler that although we believe these three conditions to be different manifestations of the same disease, yet, as clinical syndromes, they seem to us to be distinct in their natural history and course. Hence, we suggest, that the whole should be called the myotonic syndrome' and the three clinical types should be referred to as the dystrophia myotonica myotonia congenita and paramyotonia forms. There is a good deal more information but I won't take up your time with it this morning.

PRESIDENT HOOKER We have two questions from the floor the first from Dr J Loudon of New York City who asks "In Charcot Marie-Tooth disease, what per cent of siblings may contract the disease?" The other is from Dr Morton Hand, "Has Dr Tyler noted the association of peroneal muscular atrophy and facioscapular dystrophy in the same family?"

DR F H TYLER (Closing) I am interested in Dr Walton's results, and have only one or two comments in relation to them. First of all in what we have called childhood dystrophy, we have also observed a small number of cases of symptomatic onset in adolescence. However they have occurred in our series in patients scattered through the families in which typical cases occur and we have had the good fortune in at least one of these cases to have been able to exam [illegible]

[illegible] in patients with facioscapulohumeral dystrophy, occurring only less frequently with this trait

I would like to emphasize that in what I say about myotonia congenita and paramyotonia being separate diseases I would imply only in those circumstances in which it is possible to show that a large number of cases belonging to a single pedigree fail to develop [illegible]

[illegible] of the trait is approximately the expected 50 per cent. Occasional apparently isolated cases do occur. Whether they are new mutants, some other genetic mechanism or result from a non genetic mechanism [illegible]

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DISCUSSION

DR JOHN WALTON [Newcastle on Tyne, England] It gives me very great pleasure to be able to discuss Dr Tyler's paper this morning partly because of my own interest in the muscular dystrophies and partly because I am very glad to be able to congratulate Dr Tyler on his extensive work and his presentation this morning, and also on the meticulous way in which he has collected such an enormous volume of data

My own work during the last three years in the Department of Medicine in Newcastle under the direction of Professor Nattrass, was concerned particularly with the muscular dystrophies, however, I am afraid that our pedigrees for somewhat obvious reasons are very much less impressive than Dr Tyler's Nevertheless, we managed to collect information about 136 cases of muscular dystrophy of which I was able to examine 114 personally

So far as classification is concerned, I would like firstly, to mention the 'pseudohypertrophic' type which Dr Tyler described to you We have about 60 cases of this type The evidence in several families confirms his suggestion of a sex linked recessive type of inheritance, but, in common with his experience, we also discovered a large number of single cases in our pedigrees Since we believe that our series approaches complete ascertainment of the cases of myopathy in Northumberland and Durham, I think that we, too can confirm that this is a gene with a very high mutation rate

So far as this 'pseudohypertrophic type of dystrophy is concerned, our evidence for a sex linked recessive factor lies partly in the pedigrees and partly in the fact that in two families by extensive blood grouping studies we discovered that certain patients who purported to be legitimate were, in fact illegitimate In these two families there were affected males by the same mother, but by different fathers This confirmed that the disease was transmitted by the female

Our only disagreement with Dr Tyler's classification of these cases is his use of the term 'childhood' As he says the term 'pseudohypertrophic', has obvious objections since muscular pseudohypertrophy is not invariable However we feel that the term, childhood', has similar disadvantages because in three of our pedigrees showing a clearly sex linked recessive type of inheritance, the disease did not begin until late in the second or early in the third decade, and yet it still showed the characteristic clinical picture and rate of progress of the 'childhood cases which Dr Tyler has described We would prefer to call this the Duchenne type of muscular dystrophy

We would however agree completely with his classification of facioscapulohumeral dystrophy, we too have found that this condition is inherited as a dominant Mendelian trait In one family only there was some suggestion that it might be a sex limited dominant since it occurred exclusively in females

Dr Tyler mentions the juvenile type described by Dr Erb in which there is no facial involvement, and the shoulder girdle muscles are first involved In other cases the disease first affects the pelvic girdle in either instance the condition begins usually late in the second decade or sometimes a good deal later Dr Tyler feels that these cases are rare Unlike his experience we had 20 patients of this type and we feel that this is undoubtedly a separate group This form is generally transmitted as a simple recessive gene, we have called it the 'limb girdle' type

Thus, as far as our evidence is concerned we think there are three basic types of muscular dystrophy, differing genetically and clinically first, the childhood or as we prefer to call it the Duchenne type of muscular dystrophy, which is transmitted as a sex linked recessive factor, secondly the limb girdle form which is an autosomal recessive, and third, the facioscapulohumeral, which is dominant

So far as the myotonic cases are concerned, we are again in slight disagreement with Dr Tyler We have a number of families which presented with a typical picture of myotonia

CHAPTER XVIII

THE HEREDITARY ATAXIAS

JOHN W SCHUT[1]

INTRODUCTION

Of the degenerations of the central nervous system a group of inherited disorders may be designated as the hereditary ataxias These diseases have, as the basis for symptoms of incoordination, either a primary degeneration of the posterior columns of the spinal cord or the cerebellum and its neural pathways Other consistent features are the progressive nature of the affection a describable inherited tendency, its onset after birth, and its variability in clinical and pathologic features However, degeneration in the pyramidal system in the system of lower motor neurons in the brain stem and spinal cord may be associated and result in a more severe disability than coordination disorders in some families Optic atrophy may be the initial sign overshadowing signs of deficit in other areas Nevertheless the term *hereditary ataxia* is most descriptive for the term describes two features of the disease which are the most consistent in the literature

GENETICS

Friedreich (27) described the first family of hereditary ataxia in 1863 This type of ataxia according to Bell and Carmichael (7) may be recessive, dominant or sex linked Sex linkage appears in the pedigrees of Mastin (53) and Turner (83) The type of hereditary ataxia described by Friedreich usually appears before the age of 20 has absent deep reflexes and some skeletal deformity Ataxias appearing after the age of 20 usually have preserved reflexes and a dominant hereditary pattern This variety is most frequently referred to as hereditary cerebellar ataxia Bell and Carmichael (7) called this variety spastic ataxia'

These two clinical varieties of hereditary ataxia have been shown to be associated in the same pedigree with hereditary spastic paraplegia (74) Spastic paraplegia appearing independently is usually a recessive or a dominant Haldane (31) showed recessive spastic paraplegia to be determined by a partially sex linked gene, the dominant variety is probably

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CHAPTER XXIII

THE HEREDITARY ATAXIAS

JOHN W. SCHUT[1]

INTRODUCTION

Of the degenerations of the central nervous system a group of inherited disorders may be designated as the hereditary ataxias. These diseases have as the basis for symptoms of incoordination either a primary degeneration of the posterior columns of the spinal cord or the cerebellum and its neural pathways. Other consistent features are the progressive nature of the affection, a describable inherited tendency, its onset after birth, and its variability in clinical and pathologic features. However, degeneration in the pyramidal system, in the system of lower motor neurons in the brain stem and spinal cord, may be associated and result in a more severe disability than coordination disorders in some families. Optic atrophy may be the initial sign overshadowing *signs of deficit in other areas*. Nevertheless, the term *hereditary ataxia* is most descriptive, for the term describes two features of the disease which are the most consistent in the literature.

GENETICS

Friedreich (27) described the first family of hereditary ataxia in 1863. This type of ataxia, according to Bell and Carmichael (7), may be recessive, dominant, or sex linked. Sex linkage appears in the pedigrees of Mastin (53) and Turner (83). The type of hereditary ataxia described by Friedreich usually appears before the age of 20, has absent deep reflexes and some skeletal deformity. Ataxias appearing after the age of 20 usually have preserved reflexes and a dominant hereditary pattern. This variety is most frequently referred to as hereditary cerebellar ataxia. Bell and Carmichael (7) called this variety spastic ataxia.

These two clinical varieties of hereditary ataxia have been shown to be associated in the same pedigree with hereditary spastic paraplegia (74). Spastic paraplegia appearing independently is usually a recessive or a dominant. Haldane (31) showed recessive spastic paraplegia to be determined by a partially sex linked gene; the dominant variety is probably

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autosomal Since the review by Bell and Carmichael (7) in 1939 several large pedigrees have been published (33 42, 74 89, 90) Publication of these extensive pedigrees permits a comprehensive picture of the disorder with its intra family variations and mode of inheritance The pedigree reported by Beers and Cheever (5) showed hereditary ataxia determined by a partially sex linked gene with 24 per cent crossing over The evidence from four families (5 42, 74, 89) indicates a variety of dominant hereditary ataxia is partially sex linked *In addition there is an array of disorders* clinically and pathologically related which are due to mutations on the X chromosome They are sex linked Friedreich's ataxia partially sex linked recessive spastic paraplegia, progressive peroneal muscular atrophy retinitis pigmentosa, pseudohypertrophic muscular dystrophy and Leber's optic atrophy In the literature families have appeared with each one of these disorders and ataxia combined It is interesting that these related disorders are due to mutation of genes on the same chromosome It may mean that either their pathogenesis is similar or that defects in related enzyme systems underly the progressive degeneration which is common to them all This and other evidence appears to indicate that hereditary ataxia is heterogenous

The penetrance of hereditary ataxia is close to 100 per cent Rarely ataxia appears in members whose parents were apparently normal As demonstrated in the pedigrees reported by Brown (16) and Freibel (89) certain parents of the affected members were without ataxia Brain (15) attempting to explain this phenomenon postulated that the dominant gene in these families was assisted by a homozygous set of accessory genes Heredity of this type allowed for latent forms of disease and the appearance of ataxia dependent in part upon the genetic constitution of the mate Bell and Carmichael (7) mentioned a controlling factor and Haldane (32) believes a rare modifier depresses the appearance of the disease in certain instances Van den Bosch (89) mentions a family where the ataxia skipped several generations and then began to act like a completely penetrant dominant Popenoe and Brousseau (61) thought modifiers were responsible for alterations in the expression of the mutant gene causing changes in penetrance and anatomic localization of the degenerative process They extended their theory in an effort to explain abortive forms Leers and Scholz (44) enlisted the phenomenon of multiple allelism to explain variation that exists between members of separate ataxic families However inter family variation is hardly greater than intra family variation tending to show that genetic and or environmental modification is important in explanation of the diverse manifestations

Bell and Carmichael (7) who reviewed more than 1 000 cases of ataxia from the literature in 1939 present a review of the genetic characteristics

of hereditary ataxia They set up diagnostic criteria to identify inherited disease and distinguish recessive and dominant types by use of these criteria They separated three different types of hereditary ataxia, the first two types were distinguished from each other by the presence or absence of the patellar knee jerk, into categories designated Friedreich's ataxia and spastic ataxia' The third type, hereditary spastic paraplegia, was the diagnosis attached to affected individuals that had no ataxia They then made comparisons between the six groups of hereditary ataxia distinguished by these criteria From their data, it can be determined that the group designated as spastic ataxia of the dominant hereditary category had a variable age of onset A graph of onset ages showed that there were three peaks one at 10 to 14 years another at 35 and 39 years and another between 60 and 64 years The latter could be the late cortical cerebellar atrophy type as mentioned by Richter (66) These studies show the genetic type of ataxia more important in determining the age of onset than the clinical type Thus for the type of ataxia determined by the recessive gene, age at onset was usually below 20

Bell and Carmichael (7) showed the mutant gene lowered the general life expectancy by about 16 years It made little difference if onset occurred at a young age the duration was roughly the same this is not true for all reported pedigrees however (33 42) Significance was attached to the age of onset in distinguishing clinical types because a high correlation was found between the onset ages in siblings Linkage with a number of autosomal characteristics was attempted by Bell (7) and by the writer (75) No evidence was found for linkage with any of the definitely inherited

... most geneticists feel that the observable differences in the onset of the disease between parent and child is mainly due to the selection of data (75)

CLINICAL

General principles

The clinical neurologic findings which one may ...

... of symptoms and signs which distinguish it from other families This is called the biotype intra family variation will be less extensive than inter family differences Siblings often have identical clinical pictures The stage to which the ataxia has progressed will determine the neurologic findings one may expect to elicit Certain signs are characteristic of early stages others of the late stages this will be depend

autosomal. Since the review by Bell and Carmichael (7) in 1939 several large pedigrees have been published (33, 42, 74, 89, 90). Publication of these extensive pedigrees permits a comprehensive picture of the disorder with its intra-family variations and mode of inheritance. The pedigree reported by Beers and Cheever (5) showed hereditary ataxia determined by a partially sex-linked gene with 24 per cent crossing over. The evidence from four families (5, 42, 74, 89) indicates a variety of dominant hereditary ataxia is partially sex-linked. In addition there is an array of disorders clinically and pathologically related which are due to mutations on the X chromosome. They are sex-linked Friedreich's ataxia, partially sex-linked recessive spastic paraplegia, progressive peroneal muscular atrophy, retinitis pigmentosa, pseudohypertrophic muscular dystrophy, and Leber's optic atrophy. In the literature families have appeared with each one of these disorders and ataxia combined. It is interesting that these related disorders are due to mutation of genes on the same chromosome. It may mean that either their pathogenesis is similar or that defects in related enzyme systems underlie the progressive degeneration which is common to them all. This and other evidence appears to indicate that hereditary ataxia is heterogenous.

The penetrance of hereditary ataxia is close to 100 per cent. Rarely ataxia appears in members whose parents were apparently normal. As demonstrated in the pedigrees reported by Brown (16) and Freibel (82), certain parents of the affected members were without ataxia. Brain (15), attempting to explain this phenomenon, postulated that the dominant gene in these families was assisted by a homozygous set of accessory genes. Heredity of this type allowed for latent forms of disease and the appearance of ataxia dependent in part upon the genetic constitution of the mate. Bell and Carmichael (7) mentioned a controlling factor and Haldane (32) believes a rare modifier depresses the appearance of the disease in certain instances. Van den Bosch (89) mentions a family where the ataxia skipped several generations and then began to act like a completely penetrant dominant. Popenoe and Brousseau (61) thought modifiers were responsible for alterations in the expression of the mutant gene causing changes in penetrance and anatomic localization of the degenerative process. They extended their theory in an effort to explain abortive forms. Leers and Scholz (44) enlisted the phenomenon of multiple allelism to explain variation that exists between members of separate ataxic families. However inter-family variation is hardly greater than intra-family variation, tending to show that genetic and/or environmental modification is important in explanation of the diverse manifestations.

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hereditary spastic paraplegia and hereditary ataxia associated with optic atrophy where the atrophy appeared abruptly as in cases of Leber's optic atrophy and retrobulbar neuritis These observations remove a barrier existing between the optic atrophy associated with the hereditary ataxias and the optic atrophy appearing independently Apparently it bears on the interpretation of the disease process also, as have 'acute' manifestations in the course of the ataxia Such acute phenomena are rare, it is more characteristic for the symptoms to be slowly progressive

Ophthalmoplegias are sometimes associated with optic atrophy as in the family of Sanger Brown (16) Pupils that fail to react to light or accommodation are sometimes found Weakness of the external rectus muscles may be an isolated extraocular muscle weakness Involvement of the facial nerve can be bilateral or unilateral, in families where bulbar symptoms predominate weakness of the face causes alterations in expression or fasciculation (74) Eighth cranial nerve involvement appears as a sign associated with the coordinative disturbances in certain families it may be absent or associated with other symptoms appearing in the late stages When early involvement of the bulbar cranial nerves takes place changes in the character of the cough or in modulating the voice may be an early symptom Signs of involvement of the twelfth cranial nerve leads to atrophy and fasciculation of the tongue often associated with more diffuse manifestations of lower motor neuron disturbances in the bulb (74)

It was mentioned that the fifth cranial nerve was usually without change However Biemond (10) reported a family in 1947 who had in addition to a degeneration of the posterior columns extending the entire length of the cord atrophy of the cerebellum and fifth cranial nerve This combination of symptoms and pathologic findings seems to set this hereditary d... tive proc...

It ... but its occurrence is quite constant in these ataxias

Pyramidal system

A disease of the pyramidal system evidenced by hyperactive reflexes extensor toe signs or clonus is present in many forms of ataxia In the Friedreich variety a Babinski sign may be combined with absence of deep reflexes In hereditary spastic paraplegia howe...

... ement in ataxia makes it a ...acteristic feature It has been used to classify the ataxias by Bell and Carmichael (7) who employed the presence or absence of the patellar knee

ent upon the family studied For instance, optic atrophy which is characteristic of the late *stages in most families with hereditary ataxia occurred* as an initial sign in the family reported by Sanger Brown (16) Disorders such as difficulty in swallowing static tremors and muscular atrophy are manifestations of the late stages as a rule

Incoordination

Symptoms and signs of incoordination are most frequent reflecting changes taking place in the cerebellum its pathways and/or the posterior columns of the spinal cord Because of the frequency and prominence of such signs as implicate these structures the term ataxia is appropriately descriptive its semantic derivation indicates disordered movement A gait disturbance is often the first sign of cerebellar dysfunction Gross incoordination is seldom present the ataxia is mild and hypermetria minor directional errors and discontinuity and slowness of movements characterize it Violent intention tremors are rare Adiadokokinesis is seldom present in the early stages A speech disturbance may occur with other initial symptoms As with many cerebellar signs there may be intermittency influenced *by a co-existing pyramidal system disturbance*

The cranial nerves

The cranial nerves are often severely involved Of the twelve cranial nerves the first fourth fifth and the eleventh nerves are seldom affected However the second third sixth seventh eighth ninth tenth and the twelfth nerves are often involved in varieties of hereditary ataxia The *motor components of the third seventh ninth and twelfth nerves* are sometimes included in an affection of the anterior horn cells in the spinal cord or they may be involved independently The second cranial nerve is more frequently involved than others Van Leeuwen and Van Bogaert (87) discussed the association of hereditary ataxia with an affection of the optic nerve and distinguished three varieties

Leber s hereditary optic atrophy is a dominant sex linked disease which *involves the optic nerve exclusively However Ferguson and Critchley (24)* and Behr (6) report families where the prominent affection was that of a hereditary optic atrophy where certain members demonstrated in addition symptoms of ataxia Optic atrophy and ataxia appearing in the same family show a fundamental relationship between the two disorders A distinction between the two types of degenerative disorders had been made on a clinical observation that in Leber s optic atrophy the disorder appeared abruptly, *it resembled in its character of onset the optic neuritis* seen in certain varieties of multiple sclerosis Recently, however Bickerstaff (9) and Van Leeuwen and Van Bogaert (88) reported families of

ataxia They may occur in members of a family who escape the actual disease

Incontinence is sometimes a symptom of the later stages of ataxia in certain families if present in the mother or father ataxic it may be transmitted to their children (74) The sign of exophthalmos, dilated pupils and retraction of the upper eyelids, form a distinct feature of the disease in certain families An intolerance to cold is frequently present (38, 42) On the other hand, an opposite phenomenon may be present, the ataxic patient insisting that his room be kept cooler than a comfortable temperature for normal people (74) The general nutrition of the patient seemingly has no connection with the disease Marked obesity in certain cases of ataxia may interfere with ambulation while on the other hand, the patient may become emaciated There is a tendency to tachycardia constipation, and pale moist cool skin Extension of the ataxic process to the basal ganglia and related nuclei may cause rigidity or static tremors which are usually mild

ASSOCIATED CLINICAL FEATURES

A clinical pathologic feature often associated with Friedreich s ataxia is a disorder of the heart Schilero (72) reviewed cardiac abnormalities which are associated with this ataxia He performed a general postmortem on one case of Friedreich s ataxia which showed fatty necrosis of the heart a diffuse chronic interstitial myocarditis an adenoma of the pituitary and persistent thymus tissue The electrocardiogram is often diagnostic, in lead one there is a negative or isoelectric T wave In lead three, there is usually a small Q wave The same abnormalities are present in lead two In lead three an inverted T wave is seen and precordial leads show a tendency for the T wave to be inverted These ECG abnormalities were found unrelated to sex age and onset It was noted that members of the same family with Friedreich s ataxia tended to show the same ECG tracings These findings may be associated with other cardiobulbar symptoms sometimes responsible for death in Friedreich s ataxia

The incidence of associated extraneural al...

... review

...gnificance of the association and postulates which have been elicited for its explanation They dispel the theory of close genetic linkage and two separate genes appearing to favor a hypothesis which states that it is an expression of the ataxic gene operating in a different genetic environment

jerk as the sole criterion in separating two types They mention that using this clinical finding is valid because the pattern of reflex activity was established early in the course of the disease The knee jerk if hyperactive in the initial stages of the ataxia seldom changes through the course of the disease However, a hyperactive Achilles reflex may disappear in the late stages and should the disease be prolonged past the phase where this reflex begins to become hypoactive the knee jerk may also be included in this extension of the disease process The progressive involvement of the posterior columns and/or roots in the lower lumbar and sacral areas of the spinal cord is probably responsible for the late disappearance of reflexes in the lower extremities

Muscular atrophy

Muscular atrophy, reflecting changes in the anterior horn cells is very frequent Usually isolated groups of muscles are involved and this tends to be a pattern in certain families Most commonly affected are the muscles supplied by the ulnar and peroneal nerves The muscles of the upper arm and shoulder girdle may be involved Sjogren (79) in his review of ataxia in Sweden stated that muscular atrophy was common in the late stages of ataxia especially in Friedreich's ataxia

Sensation

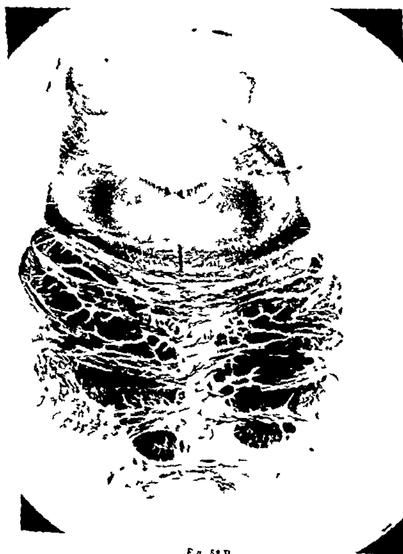
A severe disturbance in deep sensibility is usually present when all deep reflexes are absent Such a combination of symptoms is constantly present in cases of Friedreich's ataxia being a necessary clinical feature of this form Disturbances in position sense and in the perception of vibration sensibility are seen in this variety of ataxia In other forms of ataxia the disturbance in deep sensibility and position sense may occur late in the course of the disease or be a function of the duration (76) Involvement of superficial sensibility is less common spotty areas of diminished sensation to pin and cotton may be present in the feet of ataxics in the later stages of their disease The subjective sensation of pain is unusual however Klippel and Durante (41) reported prominent lumbar and gluteal pain followed by anesthesia in scattered areas of the lower extremities in certain members of the pedigree they studied

Miscellaneous clinical features

Skeletal deformities are the most common extra neural abnormality Pes cavus and scoliosis are often considered necessary clinical features distinguishing Friedreich's ataxia from the hereditary cerebellar form However, such deformities also occur in the dominant variety of hereditary

cerebellar structure wh ch usuall exclu les the flocc ilus (archicerebellum) The po terior n dl ne structures are usually unchanged al o The most severe affect on is in the superior an l lateral portions of the cerebellum This leaves free of patholog c cl ange the roof nuclei and its efferent fibers lea l ng to tl e me lulla oblongata in the juxtarestiform bo ly

2 *Tl e posterior columns* Tl is afferent sensory system of the spinal cord s degenerated in Friedreich s atax a



F g 53 B

PATHOLOGY

Even though hereditary ataxia is variable in its pathologic manifestations an indication exists that certain areas of the central nervous system are more vulnerable to the degenerative process than others. The frequency with which various systems are involved will contribute to our understanding of this disease and assist in a classification.

Distribution of lesions

1. *The cerebellum.* The cerebellum with its afferent and efferent system of neurons is the most frequently involved structure of the central nervous system. In hereditary ataxia the degeneration taking place may be primary in the cortex of the cerebellum or in the afferent neurons which lead to it. The microscopic detail will usually determine which variety of cerebellar degeneration exists. The proposed classification attempts to divide cerebellar degenerations into four different categories depending on the localization of the process in the cerebellum. Regardless of the category in which these degenerative processes are placed there is a localization within the



Fig. 53 A

Fig. 53. The salient pathologic features of olivopontocerebellar atrophy [illegible] pathologic [illegible] A. Weil [illegible] stain of the [illegible] oblongata show [illegible] body. B. De- [illegible] C. D. Disappear [illegible] nated silver. X [illegible] 275). These figures are published by the courtesy [illegible] of The Armed Forces Institute of Pathology.

disturbances Van Leeuwen and Van Bogaert (88) reported combinations of various forms of ataxia with a disorder of the basal ganglia structures, which appear in the late stages If the condition reported by Denny Brown (19) hereditary sensory radicular neuropathy, is to be included with the ataxias as a variety of peroneal muscular atrophy there exists a type which is sensory in nature However, the distribution of lesions in hereditary ataxia involve the motor system for the most part

Pathologic processes in hereditary ataxia

Orton (60) classified hereditary disorders of the nervous system into three groups differentiated by microscopic detail They are the (a) *agenetic* group characterized by congenital absence of the whole or parts, exemplified by microcephalia and including hypoplasias (b) *paragenetic* group are dysplasias or heterotopias where there is no lack of numerical development but a failure in ultimate differentiation or distribution' of neurons Both of these abnormalities may have little symptomatology and are recognized at birth as static neurologic deficits

These two types of hereditary nervous disorders are distinguished from the so called (c) *catagenetic* disorders to which hereditary ataxia belongs Clinically and pathologically there exists a sharp line of distinction between this group and the other two groups of developmental mistakes However, investigators in this field seldom insist that such a sharp distinction exists *between the anomalies or developmental* defects and the progressive degenerations of the central nervous system Even Orton (60) who suggested this group stated that this catagenetic category consists of cases in which a defective development results in degenerative changes Lewis (15) states that cerebellar maldevelopment is characteristic of Marie s ataxia ' although this pathologic change has seldom been described for it Schlesinger and Goldstein (70) state the consensus favors the origin of this neurologic disorder wholly or chiefly on the basis of an anomaly or predisposition of the central nervous system, Schaffer (71) lists several cytoarchitectonic variations as predisposing to the heredodegenerations He states that these anomalies represent a defective stratum, a micromorphologic stigma of degeneration which forms the fertile ground upon which the disease *process implants itself*

The nervous system which develops hereditary ataxia is usually developmentally sound To assume etiologic significance the developmental anomalies frequently found associated with the ataxias must be constantly present Clinically anatomic *imperfections* are discovered at birth and produce no signs of progressive neurologic *phenomena* If some developmental defect underlies the progressive degenerations total *cerebellar* agenesis should produce a progressive syndrome



Fig 53 C

3 *The pyramidal system* This afferent motor system is involved in hereditary spastic paraplegia Degeneration in this system and its combination with affections involving the cerebellum and or posterior columns has led to the term spinocerebellar degenerations first coined by Mollaret (54)

4 *The lower motor neuron* Degeneration in this system of neurons is a prominent feature in most varieties of hereditary ataxia The pattern of amyotrophy is seldom generalized in nature (67) Certain families may be characterized by having combined with the ataxic symptoms degeneration of the system of lower motor neurons supplying the peroneal musculature called Charcot Marie Tooth s disease other families may manifest degeneration of this system of neurons in the bulb For instance in the family of ataxia which the writer studied affection of the seventh tenth and twelfth cranial nerves was a prominent feature (76) On the other hand the family reported by Sanger Brown (16) was characterized by total ophthalmoplegia

5 *Other lesions* Optic atrophy is not infrequent in hereditary ataxia especially the hereditary cerebellar form An affection of the acoustic nerve is also common especially in varieties of ataxia associated with sensory

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Th[illegible]

[illegible] with the ataxias must be constantly present Clinically anatomic imperfections are discovered at birth and produce no signs of progressive neurologic phenomena If some developmental defect underlies the progressive degenerations total cerebellar agenesis should produce a progressive syndrome

The microscopic detail of the anomalies are unlike the progressive degenerative conditions of which hereditary ataxia is representative. In normal brains there is often evidence of normal variation and defects in various areas without clinical manifestations. Orton states that mentally defective individuals have (a) quantitative reduction, (b) arrest in migration and (c) arrest in differentiation of neurons. These phenomena take place in the early development of the cerebral cortex and the disordered construction has halted and long since produced its maximum clinical effects. If such gross mistakes in development fail to produce progressive degenerative features, how can the evidence of minor defects found associated with the ataxias be interpreted as responsible for the progressive degenerative process?

The micropathology of hereditary ataxia

The pathologic changes which neurons undergo in hereditary ataxia was described by Jendrassik (38), Nissl (57), Marinesco (51), Schaffer (71), Hosslin and Alzheimer (37) and Bielschowsky (12). Nissl described the chronic cell alteration, the pathogenesis of which is discussed by Marinesco and agreed to by Schaffer (71) in his work on the histopathology of the hereditary degenerative diseases. The chronic cell alteration of Nissl is characteristic of hereditary ataxia as well as hereditary optic atrophy, progressive spinal muscular atrophy, spastic paraplegia and other degenerations of the central nervous system.

The first stage of the process is swelling of the neuron which is accompanied by a loss of tigroid or Nissl substance. Marinesco (51) believed that certain insults altered intracellular enzymes causing this autolytic hydrolysis of the tigroid substance and because more molecules were produced intracellularly the osmotic pressure increased, the cell imbibed water and swelled. The process damages the cell membrane which is unable to hold the accumulated water. The cell then shrinks, the nuclei become distorted, the result is a sclerotic cell which has been changed from a rounded or pear shaped body to an angular pyramid with a narrowed, elongated elliptical nucleus staining darkly with aniline dyes. The apical dendrite is sometimes tortuous.

Schaffer (71) also describes changes in the neurofibrils of the neuron in these pathologic processes. Clumping first takes place, followed by fragmentation, and finally the fibrils break up into dust like material.

HYPOTHESES FOR THE PATHOGENESIS

Among pathologic processes enlisted to explain degenerative disorders Orton (60) mentions three possibilities in his review of the histopathology

of the hereditary degenerations (a) inanition, (b) intoxication, and (c) senility Raymond (62) is the author of the hypothesis that a precocious senility operates in the heredo-degenerations Lloyd and Newcomer (48) mention that Williamson thought the posterior lateral areas of the spinal cord in Friedreich's disease was involved because it had a different source of blood Bailey (3) showed vessels in this area were more vulnerable to age changes than others of the cord Riggs (67) discussing Wilson and Dean s paper on hereditary ataxia in monozygotic twins stated that the selective degeneration could be ascribed to localized vascular abnormalities or defects in the distribution of various blood vessels Marburg and Riese (49) also state that the distribution of lesions corresponds to certain arterial supply areas They state, a noxa' travels into these vessels Llorca and Martinez (47) discovered a developmental defect in an embryo involving the posterior columns which they thought significant in producing the lesions of hereditary ataxia The Vogts (Cecile and Oscar) have designed a theory for selective degeneration called *pathoclisis* It is based upon the observation that many toxins have a selective action such as carbon disulfide for the basal ganglia (Richter, 65) lead for the radial nerve, the tetanus toxin for the trigeminal nerve etc Gowers (30) is responsible for the term *abiotrophy* Gowers believed the degenerating tissue was developmentally imperfect had a lack of vital endurance or an inherited submicroscopic developmental defect Numerous analogies have been drawn between the phenomenon of abiotrophy and mechanical devices Edinger (22) spoke of it as a using up (Aufbruch) and Bing (13) as an effect of wear and tear on a [illegible]
deg[illegible]
of [illegible] use life is dependent upon the material of which it is made even though it may operate efficiently at first and present an identical appearance to another of better quality its true quality is discovered after use

A fundamental defect exists in such an analogy as emphasized by Lansing (43) He states that wearing out *is to* be expected of material which cannot reconstitute itself The situation, however cannot be applied to living *systems for* they have the capacity for self synthesis This property distinguishes living from non living *matter* If the living organism can and does reconstitute itself it is difficult to understand how it can wear out It is necessary *to assume* that *the* mechanism of wearing out or the aging process is due to *decreased efficiency* of some reconstruction mechanism If abiotrophy or *senescence* can be defined in specific physiologic terms it will have meaning but the terms have been convenient ones unable because of their connotations *to* stimulate experimental investigation

The initial site of lesion

Whether hereditary ataxia represents a primary disorder of the cell body of the neuron or whether the myelin sheath of the axis cylinder is the site of initial involvement is unsettled. Welte (91), van den Bosch (89) and others believe the initial site of affection to be the terminal part of the axon, describing changes of the cell body as secondary, stating they were typical of retrograde changes (chromatolysis) when the axon is cut. On the other hand, other workers in the field have entertained the theory that the degeneration commences in the neuron, the death of which causes demyelination. In certain instances, the nature of the disease has been determined as multiple sclerosis, which is considered a disease affecting the myelin sheath. Lichtenstein (46) records the differential criteria for distinguishing primary and secondary demyelination.

There is evidence to support a hypothesis that two separate disease entities exist, one demyelinating in nature, the other attacking the nerve cell primarily. Hassin (34) sought to distinguish Friedreich's ataxia from hereditary cerebellar ataxia, stating that the former was one which involved the myelin sheath, the latter the nerve cell body. In certain cases of Friedreich's ataxia there is localized demyelination within the posterior columns of the spinal cord which corresponds to the development of the myelin sheaths in the embryo, which was depicted in four different stages by Trepinski (81). The initial localization of lesions in two varieties of animal ataxia, in rabbits (1) and mice (21), was in the vestibular system, a tract which is one of the earliest to myelinate in the embryo. The order of myelination is similar to the order of degeneration according to Dickie (21). Such studies were possible by sacrificing these animals at various stages of their ataxia and noting the sequence of system involvement. These studies are to be continued in the future by attempting to detect local enzyme activity in tissues vulnerable to breakdown. This evidence tends to support the hypothesis that hereditary ataxia is a primary disease of the sheath of the axis cylinder.

The doctrine stating that the primary site of degeneration lies in the nerve cell has certain supporting facts. In certain varieties of hereditary ataxia a degeneration of the system of lower motor neurons in the spinal cord and medulla takes place; it was present in cases of the family the writer studied (76). The anterior horn cells suffered extensive destruction associated with marked glial reaction. The hypoglossal nucleus had almost disappeared, being replaced by proliferation of glia and new capillaries. The roots leading from the anterior horns were demyelinated, but primary degeneration of rootlets is seldom accompanied by glial reaction around the cell bodies. The changes resembled those of poliomyelitis, recognized as a primary nerve cell disease. The distribution of the lesions does not

resemble diseases recognized as primarily demyelinating (as in multiple sclerosis) but there was a more selective involvement corresponding to the muscular atrophy detected clinically

Clinically a salient feature detected in all but a few members of the genealogy studied by the writer was a fasciculation of the tongue Other musculature was affected similarly prior to atrophy This clinical neurologic sign was interpreted as a cellular phenomenon because it is seldom seen in peripheral neuritis or disease of the sheath of the axis cylinder

CLASSIFICATION

The subject of classification of the hereditary ataxias is a difficult feature of this study Many factors have contributed to the inconsistencies present in the attempt of investigators to group the ataxias under appropriate nosological categories Although rare the hereditary ataxias have had sufficient studies and the reports in the literature have been extensive enough to allow an understanding of its clinical pathologic, and genetic features

Inherent in the ataxic disease process and part of its definition is its *variability* Certain systems are more likely to degenerate in the hereditary ataxias than others but the sequence of involvement may be altered causing one system to degenerate before the other The same gene may be responsible for several different clinicopathologic entities depending upon the site of localization Whereas the actual existence of the disease is caused by a mutant gene the distribution extent and severity of the le on are

... ways it would also influence attempts at classification

In describing hereditary ataxias a group of consistent clinical and pathologic criteria should be established Refusal of one gro in of ...

... it is be all that is necessary to allow for comparisons as for instance the presence or al ...

... t exists in regard to the mode of inheritance of the ataxias can be traced to th ...

conclusions after a review of the same disease These opposing conclusions can be traced to the use of *different criteria to separate groups of ataxia*

A suitable classification for the ataxias or any genetic disease with varied manifestations may be delayed until the primary etiologic agent is discovered It will then be possible to group with it *identical disease processes* instead of diseases producing similar distribution of lesions in the central nervous system A classification of this nature would be on sound ground but it would entail establishing not only the chromosomal loci of the mutated gene the type of mutation and the mechanism of producing lesions as well For this reason such a classification is premature at the present time

There exist certain static genetic criteria upon which a fundamental division of hereditary ataxia can be made (i e *recessive dominant sex linked* or *partially sex linked*) All geneticists agree upon the characteristic distribution of disease present when ataxia is dependent by one of these determiners Such a division may be arbitrary for some investigators as it employs genetic criteria which, however are less variable than clinical and pathologic data For ataxias where the mode of inheritance cannot be determined for lack of numbers or where typical manifestations of the disease seems to appear independent of heredity an undetermined category should be designated which will include the sporadic cases and others demonstrating atypical inheritance Bell and Carmichael (7) were the first to suggest a division of the ataxias into recessive and dominant categories They stated that such a division often determined the clinical type also suggesting to them that it may be a fundamental one

Another fundamental partition is one that involves the sequence or localization of lesions in the central nervous system *Three varieties are* recognized depending upon whether the posterior columns (Friedreich s ataxia) the cerebellum and its pathways (hereditary cerebellar ataxia) or *the pyramidal system (hereditary spastic paraplegia)* is the earliest and severest involved Because for each of these types it is characteristic to be combined with each other a pure form and intermixtures will be recognized dependent upon whether the disease is typical or atypical

In the formulation of this classification for the hereditary ataxias little has been mentioned concerning the evolution of concepts A complete consideration of the subject is beyond the scope of this paper however pertinent works on the subject should be mentioned Besides Friedreich s (27) and Marie s (50) original description of two fundamental varieties of ataxia Mollaret (54) was the first to include hereditary spastic paraplegia and an abortive variety of Friedreich s ataxia called Roussey Levy s disease with the ataxias An extensive bibliography is present in his work for those who care to review his concept in regard to the initiation of the term spino

cerebellar degenerations (55) Hassin and Harris (35) extended our viewpoints in regard to the hereditary ataxia showing as others have subsequently that olivopontocerebellar atrophy is frequently a variety of hereditary cerebellar ataxia Bertrand (8) does not include this pathologic variety with the ataxias Cortical cerebellar atrophy is a variety of hereditary cerebellar ataxia as shown by Richter (66) Lichtenstein (46) recognizes these two forms of hereditary ataxia but, because of the variation of these degenerative diseases he prefers a broad general grouping for the remainder under the term, *polymorphous neuroabiotrophies** Welte (91) used the term, spino ponto cerebellar atrophy for a recent pathologic classification of hereditary ataxia To Bell and Carmichael (7), however, belong the credit for separating for the first time genetic entities Van Bogaert (85), has contributed extensively to our understanding of these degenerations In a personal communication (86) he suggested a classification which recognizes seven forms of hereditary ataxia In a recent article the writer (76) dealt with the development of concepts in regard to the pathologic classification of hereditary ataxia

A classification for hereditary ataxias is proposed in outline following Intermixtures or combinations with other heredo-degenerations and specific clinical pathologic entities are included in a special category The proposed classification has been designed to furnish a framework on which the structure of hereditary ataxia can be built No effort was made to make the list of intermixtures or combinations complete but the classification allows for description of new and novel combinations which is characteristic of this disease entity

Classification of the Hereditary Ataxias

I Recessive
  A Friedreich's ataxia
    1 Pure form—ataxia onset before 20 absent deep reflexes skeletal deformities Degeneration of the posterior columns
    2 Intermixtures or combinations with
      a C[illegible]
      b Optic atrophy [illegible]
      c Charcot
      d Diabetes
      e Status dysraphicus
      f Retinitis pigmentosa
      g Progressive muscular atrophy
      h Progressive bulbar palsy

* This term was first coined by Dr Roland Mackay

i Dementia, oligophrenia
j Cataracts
k Striatal syndromes
l Hereditary sensory neuropathies (Denny Brown, 19)
m Roussey Levy's disease

B Hereditary cerebellar ataxia
1 Pure form—ataxia, onset after 20, preserved deep reflexes Degeneration of the cerebellum and/or its pathways
2 *Intermixtures, or combinations, with—*
a Other forms of ataxia—ataxias that are combined with posterior column degeneration and/or pyramidal tract degeneration
b Optic atrophy, cochlear involvement
c Etc (see above under Friedreich's ataxia for possible intermixtures and combinations)

C *Hereditary spastic paraplegia*
1 Pure form—onset with pyramidal tract disorder in lower extremities, minimal or no ataxia Degeneration of the pyramidal system
2 Intermixtures or combinations, with
a Other forms of ataxia—ataxias having either posterior column degeneration or degeneration of the cerebellum and its pathways
b Optic atrophy
c Etc (refer above to combinations with disorders mentioned under Friedreich's ataxia)

II Dominant or dominant partially sex linked
A Friedreich's ataxia
1 Pure form—ataxia onset before 20, absent reflexes skeletal deformities Degeneration of the posterior columns
2 Intermixtures or combinations with
a Other forms of ataxia
b Etc (see above for possible combinations)

B Hereditary cerebellar ataxia
1 Pure form—ataxia onset after 20 preserved deep reflexes
Degeneration of the cerebellum and/or its pathways
a Olivopontocerebellar atrophy (Hassin and Harris 35, Waggoner et al, 90)
b Cortical cerebellar atrophy (Richter 66)
c Spino cerebellar tract degeneration (Rydel 68, Barker 4)
d Degeneration of the brachium conjunctivum and dentate nucleus (Welte 91 etc)
2 Intermixtures or combinations with
a Other forms of ataxia
Friedreich's ataxia—combinations of the above pathologic entities with posterior column involvement
Spastic parapelgia—pyramidal system involvement associated with the above cerebellar conditions
b Progressive muscular atrophy
c Progressive bulbar palsy
d Etc (see previous list for possible combinations)

C Hereditary spastic paraplegia
1 Pure form—minimal or no ataxia onset with pyramidal system disorder in lower extremities, degeneration of the pyramidal system

5 Intermixtures or combinations, with
  a Other forms of ataxia
    Friedreich s ataxia
    Hereditary cerebellar ataxia
  b Optic atrophy
  c Etc (see under Friedreich's ataxia for other possible combinations)

III Sex linked or recessive partially sex linked ataxia
  A Friedreich s ataxia
  B Hereditary cerebellar ataxia
  C Hereditary spastic paraplegia
    (A pure and a mixed form may be recognized for each of these categories also, in the literature a sex linked variety of Friedreich s ataxia 53 83 has been described and the recessive variety of spastic paraplegia has been determined to be partially sex linked in its mode of inheritance 31)

IV Sporadic or ataxias with atypical inheritance

GENETIC MECHANISMS IN INHERITED DISORDERS

Gene activity

Genes have been shown to be complex nucleoproteins which have the property of self duplication There is also a tendency to mutate or change, and altered chemical action results Genes can be thought to direct development and another function that has to do with chemical activities after construction of the organism is complete Many examples of gene controlled chemical reactions have been documented in Neurospora, the best example in man is where hydroxylation of phenylalanine fails to occur as a result of a mutated gene

Genes direct these chemical events through the construction of specific enzymes, antibodies, or proteins A mutated gene does not lose its function

... has been secured from experimental genetics, which have shown that an enzyme produced by the mutated gene may be responsible for diminished intensity of a certain chemical reaction (17) This altered enzyme seems in certain instances to cause misdirection of chemical synthesis as Klent ...
disease
sickle
instead
pathology

How a ... affects kidney threshold to uric acid has been shown by Friedman and Byers (26) The Dalmatian Coach hound differs from other dogs by excreting uric acid instead of allantoin, shown by Onslow (59) to be inherited as a dominant The defect is in the inability of the Dalmatian dog to reabsorb uric acid through the kidney tubules,

for tying the ureters of these dogs allowed them to excrete allantoin like other dogs. Rimington (64) states this defect may not only be in kidney tubule cells but extends to hepatic cells—an abnormal inherited permeability defect to a specific chemical substance.

Recently Gibson (29) obtained evidence for a deficiency in an enzyme system in a familial methaemoglobinemia identified as 'coenzyme factor I.' Methylene blue corrects this defect in vivo and in vitro. This is an instance where a direct relationship exists between genetic mutation and a defect in an enzyme system.

Familial periodic paralysis is a dominant hereditary disorder due to a disorder in potassium metabolism. Periodic paralysis, occurring at irregular intervals precipitated by insulin or glucose, is characteristic of the disease. Low serum values of potassium exist during an attack, a depressed excretion of potassium antedates the attack, and the paralysis promptly disappears with administered potassium. Biemond (11) reported one family and mentions two others with this condition where certain members had muscular atrophy in addition. The paralysis occurred less frequently among those individuals having severe atrophy. The exact mechanism that produces paralysis in this hereditary disorder is unclear. Fenn (23) postulated a defect of the "sodium pump," the hypothetical mechanism that keeps sodium from the interior of the cell. The relationship that potassium has to carbohydrate metabolism is probably involved as is the abnormal distribution of the ion evoked by intake of glucose or insulin. Danowski and Tarail (18) mention that Jantz found the nonionizing portion of potassium to be decreased during attacks, as though abnormal binding of the ion took place. The genetic mechanism by which this mutation evokes a low serum level of potassium ought to be explained on the basis of recognized abnormal activities produced by mutated genes. Inasmuch as genes produce (a) specific protein moieties (as in the blood groups), (b) influence kidney threshold, or (c) produce specific enzymes, one of these defined activities of genes could operate in familial periodic paralysis. Abnormal binding of the potassium ion could result from the production of an abnormal protein produced as a result of genetic mutation.

A similar hypothesis has been suggested (20) to explain the abnormal copper metabolism in hepatolenticular degeneration. Binding of copper is accomplished in normal human sera by ceruloplasmin, a protein constituting about 0.5 per cent of the plasma proteins. Scheinberg and Gitlin (73) found this protein deficient in patients with hepatolenticular degeneration, believing this to be the primary defect. Free copper is present in the blood in too great quantities as a result, and its accumulation in vulnerable tissues has been postulated as producing the lesions (20). These authors also believe

that the absence of thromboplastin in hemophilia is a similar genetic mechanism

Familial periodic paralysis and hepatolenticular degeneration are inherited disorders of potassium and copper metabolism that may be similar in one aspect Abnormal concentrations of these ions could result from inappropriate binding to specific protein moieties rendered abnormal in structure or concentration through genetic mutation

Genetic mutation has been shown to involve chemical events in humans and animals By analogy the mechanism by which hereditary ataxia produces lesions could be similar in some way to the illustrations cited These examples tend to demonstrate a one-to-one relationship between the abnormality produced and the genetic mutation Whereas a mutated gene may be responsible for a disease with different symptoms and signs, and diverse distribution of lesions each structure involved must be related in some fundamental manner

ATAXIA AND AGING

The precocious senility hypothesis of Raymond (69) *proposed by him as* the important pathologic process in the hereditary ataxias has been accepted in principle by Orton (60) and O Leary (58) Senescence as *defined by Lansing (48)* is a dynamic process not a wearing out in the sense that

D ... at ... is aged alike in spite of different en...

... the ... ataxia with those produced by aging has been made by many *investigators* Age changes in the central nervous system have been described by O *Leary (58)* and Bailey (3) Marinesco (51) stated the chronic cell change characteristic of heredo-degenerations was similar to the cellular changes in senile brains Orton (60) mentions the diffuse paling of *myelin sheaths* in the *sacral* and lumbar segments of the spinal cord in *aging as present in* ...

... au and Gill (49) The skin changes of the ataxic are similar to those seen in aging *individuals* Age changes are also seen in the facial expression which appears to mature quickly It has been noted that some ataxic individuals appear older than their actual age A progressive loss in the perception of the sense of vibration is sometimes

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ataxia (76) has been observed in certain instances Lesions in this area may affect the nourishment of the Purkinje cells It is interesting in this connection that Richter (66) reported a family of cortical cerebellar atrophy appearing mainly in women approaching the senium There were local lesions of cerebellar cortex involving the Purkinje cells and the dentate nucleus The type of inheritance in this ataxia is dominant, however its appearance in women may be related to their more important role in regulation of calcium metabolism

Garland and Moorhouse (28) reported a family affected with a rare hereditary syndrome characterized by ataxia of cerebellar origin, cataract and poor skeletal development The disorder was due to a recessive gene apparently It had been previously reported by Marinesco (52) in 1931 and Sjogren in 1947 who reviewed other families from Sweden Some calcium determinations were performed by Marinesco who reported low values In these families a combination of cataracts deformities and ataxia suggests a relationship between calcium metabolism and the pathogenesis of the disease

Foley (25) reported a case of a woman aged 60 who had cerebellar symptoms She and her two daughters had a symmetrical calcification of the
1

[illegible] This report re-emphasizes the vulnerability of the dentate and striatum in calcification

Salter (69) states the first symptom of calcium intoxication is altered reflexes concerning posture Himwich (36) mentions the influence of enzyme activators and inhibitors with age, and also correlated them with phylogenetic development The mechanisms maintaining reflexes regulating the erect posture are a late morphologic addition to the central nervous system and as such are likely to be more vulnerable to enzyme inhibitors The irritability of the central nervous system produced by calcium deficiency is evidence that the function of the central nervous system is dependent upon a closely regulated ionized calcium level

T
the
tion
sho [illegible] ...ugal (48) has [illegible] as a tendency to appear in the dentate nucleus striatum and cerebellum but the appearance [illegible]

[illegible] can be doubled in any animal accompanied by calcium Carpopedal spasms seen in hypocalcemia or hyperventilation alkalosis fail to occur in hypopotassemia Sodium

seen in the aged, a symptom of dysfunction of the posterior columns a central nervous system structure which seldom escapes involvement in the ataxias

A systematic study of the aged spinal cord was made by Bailey (3) who mentions as characteristic the following histopathologic findings (a) gliosis increased with age, especially in the fasciculus gracilis, it was found in 12 of 15 cases that were past the age of 80 years Age changes in blood vessels were more prominent in the posterior part (b) Corpora amylacea were increased (c) Deposition of calcium took place in the meninges which were frequently thickened (d) Other investigators reported a shrunken spinal cord (e) Pigment atrophy of the ganglion cells

Many of these pathologic lesions associated with age are similar in both type and distribution to those of ataxia, especially (a), (b) and (d) However, the selection of systems that the pathologic process of ataxia chooses constitutes an objection to the hypothesis Age changes may occur simultaneously *in all tissues but its consequences are selective* because some organs manifest dysfunction before others Arcus senilis and retraction of gums are symptomless but a similar degree of age change in the posterior columns may produce difficulty in walking in the dark O Leary (53) believes aging is selective mentioning many intellectually alert old men who have signs of other regressive senile changes Further evidence that the process of aging and ataxia are similar in their distribution of lesions is their tendency to attack functions and structures which have developed late in our phylogenetic development

Relationship of calcium to the ataxic and aging processes

Lansing (43) places much significance on the role of calcium in the aging process Mobilization of calcium from bony stores takes place in aging Aging is often associated with deposition of calcium in various areas of the body (3) membrane permeability *is altered and bones become osteoporotic* (56, 78) The influence of the sex steroids especially estrogens is very important in the metabolism of calcium (56) Salter (69) mentions that estrogens are more directly related to calcium metabolism in the fowl where *the egg*

por

skeletal formation of the fetus The growth and parathyroid hormone a vitamin D also affects the distribution of calcium (56)

Calcium metabolism may be implicated in some varieties of hereditary ataxia Sugar (78) reviewed the influence of hypoparathyroidism on the central nervous system stating that pathologic lesions present in the brain *of these* individuals are often localized in the capillary walls of the cerebellum A similar localization of the pathologic lesion in cases of hereditary

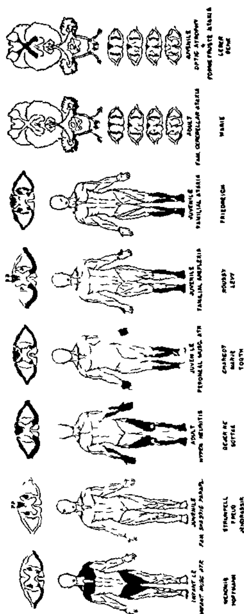

JUVENILE
FAM. SPASTIC PARAPL.
ADULT
HYPER. NEURITIS
PERONEAL MUSC. ATR.
CHARCOT
MARIE
TOOTH
JUVENILE
FAMILIAL AREFLEXIA
ROUSSY
LEVY
JUVENILE
FAMILIAL ATAXIA
FRIEDREICH
ADULT
FAM. CEREBELLAR ATAXIA
MARIE
JUVENILE
OPTIC ATROPHY
FORME FRUSTE ATAXIA

Fig 54

inhibits glycolysis by stimulating apyrase, an enzyme which breaks down ATP, thus decreasing the amount of ATP (adenosine triphosphate) available for esterification (84) On the other hand potassium has the opposite effect partially the result of its influence on the enzyme pyruvic phosphoferase (14)

Knowledge that has recently been acquired through experimental biochemical genetics has elucidated some mechanisms whereby mutant genes produce disease, it has narrowed fields of endeavor in searching for the etiology of hereditary ataxia

DISCUSSION

DR STANLEY COBB [Boston Mass] In 1933 Aring and Cobb working on the neurological wards of the Boston City Hospital saw an unusual series of patients suffering from 'primary' muscular atrophy This experience was synthesized and led to their paper in *Medicine*[2] in 1935 where these diseases were classified under the headings 'sporadic' or 'familial' The familial group was then divided into disorders where (a) the lesions are primarily in the muscles (myopathic) or (b) primarily in the nervous system (neural' or 'myelopathic) The various syndromes were described clinically and discussed from the biological standpoint It was emphasized that few diseases are so confusing to the physician as the muscular atrophies These conditions have been described under such varying titles and with such neurological meticulousness that only the specialist can be expected to keep the different syndrome clearly in mind Too often even the neurologist merely describes the clinical picture and attaches to it a name without seeing its biological relationship to other syndromes

In that earlier paper we classified the familial myopathies as follows

- Primary muscular atrophy
  - Sporadic
    - Amyotonia congenita
    - Progressive muscular atrophy
    - Amyotrophic lateral sclerosis
  - Familial
    - Myopathic
      - Myasthenia gravis
      - Family periodic paralysis
      - Progressive muscular dystrophy
      - Myotonia
      - Dystrophia myotonica
    - Myelopathic
      - Infantile muscular atrophy
      - Hypertrophic neuritis
      - Peroneal muscular atrophy
      - Familial ataxia

Since then new syndromes have been described that would come under myelopathic but because these not only include cases with lesions of the spinal cord but also of the brain it has been decided to use the term neural rather than myelopathic To the neural group have been added four more main syndromes familial spastic paralysis familial areflexic cerebellar plus spinal ataxia and optic atrophy plus familial ataxia (fig 54) A family with three cases of areflexia is described in which two cases came to autopsy giving the pathology

[2] Aring C and Cobb S Muscular atrophies and allied disorders Medicine 1935 *14* 77 See also Cobb, S and Bereday M Trans Amer Neurol Assn 1953

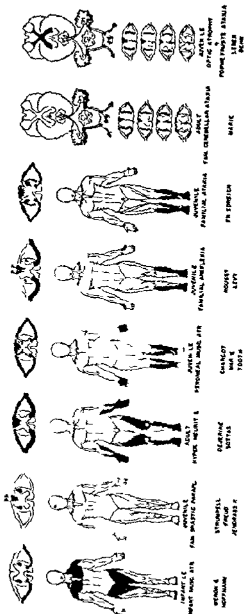

INFANT LE
INFANT MUSC ATR
JUVENILE
FAM SPASTIC PARAPL
STRUMPELL
FREUD
ADULT
HYPER NEURIT
DEJERINE
SOTTAS
JUVENILE
PERONEAL MUSC ATR
CHARCOT
MARIE
TOOTH
JUVENILE
FAMILIAL AREFLEXIA
ROUSSY
LEVY
JUVENILE
FAMILIAL ATAXIA
FRIEDREICH
ADULT
FAM CEREBELLAR ATAXIA
MARIE
OPTIC ATROPHY
FORME FRUSTE ATAXIA

Fig 54

of this syndrome for the first time This was found to be hypertrophic neuropathy with slight demyelination in the pyramidal and dorsal tracts

It is emphasized that these eight main syndromes only represent the more common examples of a large group of clinical pictures that have been described These syndromes seem to be the functional results of various combinations of eighteen localized lesions in the neuraxis. These eighteen lesions can be listed as

1 Retinal degeneration (R)
2 Optic atrophy (O)
3 Midbrain lesion with pupillary dysreflexia (P)
4 Oculomotor nuclear lesions (Q)
5 Cerebellar atrophy, nuclear (C 1)
6 Cerebellar atrophy, pontile (C 2)
7 Cerebellar atrophy, olivary (C 3)
8 Cochlear degeneration (H)
9 Degeneration of dorsal tracts of the cord (D)
10 Degeneration of cerebellar tracts (A)
11 Degeneration of pyramidal tracts (B)
12 Degeneration of ventral horn cells (V)
13 Radicular neuropathy (N 1)
14 Hypertrophic neuropathy (N 2)
15 Scoliosis
16 Pes cavus
17 Epilepsy
18 *Dementia*

(The letters in parentheses refer to the code in figure 55) The last four may be secondary manifestations so are only listed tentatively

Different combinations of the first fourteen of these lesions have caused the great variety of syndromes described in the extensive literature Our search has brought to light descriptions which might indicate more than 50 different combinations the most distinctive being

1 Infantile muscular atrophy (Werdnig Hoffmann)
2 Familial spastic paralysis (Strumpel Freud Jendrassik)
3 Hypertrophic neuropathy (Dejerine Sottas)
4 Peroneal muscular atrophy (Charcot Marie Tooth)
5 Familial areflexia (Roussy Levi)
6 Familial ataxia (Friedreich) with optic atrophy (Behr)
7 Cerebellar ataxia (Marie) with or without optic atrophy
8 Optic atrophy (Leber) with #2 #3 #4

More rarely deafness pupillary areflexia and retinitis pigmentosa are found in combination with one of the eight listed

Several authors have tried to describe new diseases' without pathological data and without understanding that in hereditary diseases the genotype (*abnormality of the genes*) may be relatively constant whereas the phenotype (clinical manifestation) may vary greatly according to developmental and environmental influences It is this kind of making of new 'disease entities' and syndromes which has so complicated neurological literature that one cannot see the forest for the trees This group of neural myopathies should be looked on as one disease with many variants Many have been already described but many more will arise and should not then be listed as new but as expected and predictable on genetic grounds

Dr Roland P Mackay [Chicago Illinois] I am very glad to comment on Dr Schut's interesting paper However Dr Cobb has so well stated what I wished to say that perhaps mine is only a perfunctory discussion

50 MOST PROBABLE COMBINATIONS

O	OC	OHC	OBHC	
R	CQ	OBH		
	OQ	OQC		
P	RH	OQR		
Q	BQ	BQO		
C	ND	NDV	ONDV	
		BDV	BDVN	
H	BV	DVH		
B	OB	OBD		
	BO	NBD	PNDB	
	AB	PDV		
	DV	DVN		ODABC
	NH	PND	DABC	DABVH
		CBR		
		CRH	DABV	DABCV
		OBN	DABH	DABHR
		DAB	ODAB	QDABC
		DAV	QDAB	

Fig 93 A cerebellar tract degeneration B pyramidal tract degeneration, C1, cerebellar atrophy nuclear C2 pontocerebellar C3 olive-cerebellar, D, dorsal tract degeneration, H, cochlear degeneration N_1 hypertrophic neuropathy N_2 root neuropathy, O, optic atrophy, P midbrain lesions with pupillary disorders, Q midbrain lesions with ophthalmoplegia, R retinal degeneration V ventral horn cells

C B H O P and Q may occur alone but combinations, as listed, are more commonly found

As Dr Cobb showed you if we discard all diagnostic categories and simply consider the anatomical substrates of various clinical symptoms and signs that we see in the familial neurologic disorders we can construct a vast panel of items of clinical abnormality Now the clinical syndromes which we commonly recognize such as Friedreich's ataxia, the Charcot Marie-Tooth type of atrophy olivo-ponto-cerebellar atrophy, etc represent only somewhat variable constellations of these items in the panel. There are so many intermediate groupings and so much overlapping between these various constellations, that neurologists are always

getting into arguments as to whether a given case represents the atrophy of Charcot Marie Tooth, or Friedreich's ataxia, or what not As has been shown in the recent studies from Guam, certain types of neurological disease, such as amyotrophic lateral sclerosis which are usually not considered familial, may, in fact, become familial in some cases and under certain circumstances

This concept, I may boast, occurred to me quite independently of Dr Cobb's formulation and I have even devised an atrocious name for this whole group of familial neurologic disorders The term is polymorphous neuro abiotrophy, intended to cover the whole group Thus we may avoid this troublesome task of classification if we simply recognize the infinite variability possible in such a genetic group We would then simply consider each patient as we see him, as representing a certain constellation of genetic defects

Contrary to Dr Schut's experience, I have never seen I believe the concurrence of a dystrophy and one of these familial neuro-abiotrophies I do not think therefore, that it is very likely that the genetic defects upon which the two types of disorders are based can be in any way similar or closely related to each other They must reside at some distance from each other in the same chromosome or perhaps even in different chromosomes

PRESIDENT HOOKER We have a question from the floor, from Dr Russell Myers of Iowa City 'Does Dr Schut identify pyramidal tract with pyramidal system and if not, precisely what does he mean to include and exclude when he employs the term 'pyramidal system'?'

DR JOHN W SCHUT (Closing) I want first to thank Drs Cobb and Mackay for their discussion Time prohibits any elaborate comment on their pertinent statements In their remarks as well as in my presentation emphasis was placed on the marked variability of the hereditary ataxias and how this has interfered with a suitable classification Many of us are tiring of the many futile attempts of prominent investigators to describe distinct nosologic entities In spite of this there are a suitable number of cases presenting typical clinical pathologic, and genetic features which serve as prototypes with which other cases not so typical can be placed The disease however is so rare that grouping around these prototypes has not assumed any significance Only time which will bring with it new studies and further observations will assist in formulating a suitable classification

In answer to Dr Myer's question I would like to state that when I referred to degeneration of the pyramidal system I implicated involvement of a particular functional group of neurons much as one would refer to the system of lower motor neurons of the medulla and spinal cord In this definition I would like to emphasize *functional* however for the exact anatomic localization of neurons producing this stereotyped set of symptoms has not been identified for the ataxias Corticospinal or corticobulbar is probably a more appropriate term for it is a system of neurons descending from the cerebral cortex influencing the final common pathway Most of these fibers travel in the pyramidal tract of the medulla oblongata although this tract probably contains fibers of subcortical origin also Less than half the fibers of this tract arise from area 4, many of cortical origin arise from unknown areas Nevertheless the neurologic signs associated with a disorder of this system produce a constant and well known syndrome

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getting into arguments as to whether a given case represents the atrophy of Charcot Marie-Tooth, or Friedreich's ataxia, or what not As has been shown in the recent studies from Guam, certain types of neurological disease, such as amyotrophic lateral sclerosis which are usually not considered familial, may, in fact, become familial in some cases and under certain circumstances

This concept, I may boast, occurred to me quite independently of Dr Cobb's formulation and I have even devised an atrocious name for this whole group of familial neurologic disorders The term is polymorphous neuro abiotrophy, intended to cover the whole group *Thus we may avoid this troublesome task of classification if we simply recognize the infinite* variability possible in such a genetic group We would then simply consider each patient as we see him as representing a certain constellation of genetic defects

Contrary to Dr Schut's experience I have never seen I believe, the concurrence of a dystrophy and one of these familial neuro abiotrophies I do not think therefore that it is very likely that the genetic defects upon which the two types of disorders are based can be in any way similar or closely related to each other They must reside at some distance from each other in the same chromosome or perhaps even in different chromosomes

PRESIDENT HOOKER We have a *question from the floor from* Dr Russell Myers of Iowa City "Does Dr Schut identify pyramidal tract with pyramidal system and if not, precisely what does he mean to include and exclude when he employs the term 'pyramidal system'?"

DR JOHN W SCHUT (Closing) I want first to thank Drs Cobb and Mackay for their discussion Time prohibits any elaborate comment on their pertinent statements In their remarks as well as in my presentation emphasis was placed on the marked variability of the hereditary ataxias and how this has interfered with a suitable classification Many of us are tiring of the many futile attempts of prominent investigators to describe distinct nosologic entities In spite of this there are a suitable number of cases presenting typical clinical pathologic and genetic features which serve as prototypes with which other cases not so typical can be placed The disease however is so rare that grouping around these prototypes has not assumed any significance Only time which will bring with it new studies and further observations will assist in formulating a suitable classification

In answer to Dr Myer's question I would like to state that when I referred to degeneration of the pyramidal system I implicated involvement of a particular functional group of neurons much as one would refer to the system of lower motor neurons of the medulla and spinal cord In this definition I would like to emphasize *functional* however for the exact anatomic localization of neurons producing this stereotyped set of symptoms has not been identified for the ataxias Corticospinal or corticobulbar is probably a more appropriate term for it is a system of neurons descending from the cerebral cortex influencing the final common pathway Most of these fibers travel in the pyramidal tract of the medulla oblongata although this tract probably contains fibers of subcortical origin also Less than half the fibers of this tract arise from area 4 many of cortical origin arise from unknown areas Nevertheless the neurologic signs associated with a disorder of this system produce a constant and well known syndrome

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CHAPTER XIX

SEIZURES, BRAIN WAVES AND INTELLIGENCE TESTS OF EPILEPTIC TWINS

WILLIAM G. LENNOX AND DONALD H. JOLLY[1]

Heredity in epilepsy has been a controversial subject since the time of Hippocrates. Our evidence on the subject is from two sources.

First is the incidence of epilepsy among the members of the epileptic's immediate family as already presented by one of us (1). A group of 4,231 patients seen in office or clinic had 20,000 near relatives. Among these 3.2 per cent had a history of one or more seizures. A sampling disclosed that approximately one half had experienced only one or two. The remaining 1.6 per cent is three times greater than the incidence of chronic epilepsy, 0.5 per cent, in the population of draft age in the United States. If epileptics had evidence of brain damage prior to the first seizure (symptomatic epilepsy) 1.8 per cent of the relatives had experienced one or more seizures. If the patient had no evidence of prior brain damage (metabolic epilepsy) the incidence for all ages was twice as great, namely 3.6 per cent. In the metabolic group the incidence of epilepsy among relatives declined progressively with increasing age of the patient at the time of the first seizure. Thus 6.4 per cent of near relatives were affected if the epilepsy of the patient began in infancy but only 1.3 per cent if it began at 30 years or later, a ratio of five to one. Alstrom (2), the Swedish geneticist, found an incidence in Sweden not significantly greater than that of the incidence in the male population of draft age of the United States. The fact that his patients began to have seizures relatively late in life would account for the discrepancy between his results and ours. In ours 57 per cent had the initial seizure before the age of 10. Our second source of evidence, the subject of this presentation, is a study of 173 twins with a history of seizures.

This paper is a progress report on a twin study begun nearly 20 years ago. Previous reports have dealt with 66 (3) and 122 (4) pairs of twins

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TABLE 25

Distribution of twin propositi by sex and zygosity of propositi and by sex of co-twin with expected numbers based on a sex ratio of 54 males to 46 females found in 4000 epileptics and assuming one third of all twins are monozygotic

Twin Propositi	Observed	Expected	χ^2	Male Co-twins O	Male Co-twins E	Male Co-twins χ^2	Female Co-twins O	Female Co-twins E	Female Co-twins χ^2
Male propositi									
in MZ pairs	30	31.1	0.04	30	—	—	—	—	—
in DZ pairs	48	62.2	3.24	25	31.1	1.20	23	31.1	2.11
Total Males	78	93.3	2.56	55	62.2	0.83			
Female propositi									
in MZ pairs	47	26.5	15.9	—	—	—	47	—	—
in DZ pairs	48	53.1	0.40	16	26.5	4.31	32	26.5	1.14
Total Females	95	79.6	2.98				79	53.1	12.6
Total propositi	173			71			102		

of 117 propositi found to be twins after referral as epileptic 47 were monozygotic and 70 were dizygotic the corresponding distribution of 56 referred with knowledge of our twin study was 30 and 26 respectively The sex ratio of the groups was the same The significant excess of monozygotic pairs in the second group indicates that selection did indeed operate and to some extent has biased our sample

Table 25 shows a grouping of 173 propositi by sex and by zygosity with the sex distribution of the co twins for each group Expected numbers have been calculated on the basis of the sex ratio of 54 males to 46 females found in 4000 epileptics of all ages (7) and on the assumption that one third of all twins are monozygotic (11) Of the 173 propositi 78 were male and 95 female By χ^2 test these figures are probably significantly different from the expected values of 93 4 males and 79 6 females (02 > P > 01) indicating a relative deficit of male twin propositi

Of the male propositi 30 proved to be monozygotic and 48 dizygotic of whom 25 had a co-twin of the same sex and 23 a co twin of the opposite sex Among the female propositi 47 belonged to a monozygotic pair and 48 to a dizogotic pair Of the latter group 32 were of like sex and 16 were of opposite sexes Comparison of the observed ...

... sex ratio of monozygotic pairs (30 males to 47 females) compared with the sex ratio of *like sexed* dizygotic twins (25 males to 32 females) shows no significant difference (30 > P > 20)

The total now numbers 200 but 27 pairs have not been fully processed A valuable feature of the study is its longitudinal nature Helped perhaps by the fact that examinations and medical advice have been without charge most of the twins have been followed for many years and electroencephalograms repeated at intervals In addition to the data on 51 twin pairs not previously reported new and more detailed information has been obtained on many of the earlier cases This has made possible a more accurate classification of some pairs and has enhanced our understanding of intrapair variations During the past two years the scope of the project has been expanded to a twin family study by including detailed examination of the seizure history the E E G s and the blood groups of parents and siblings

Of the 346 persons in the study, all but 57 were seen and examined personally The attending physician supplied the needed information about these Electroencephalograms of both twins were secured for all but 11 of the pairs Three pairs had been reported by others (4 5 6)

The decision respecting zygosity was based on the usual physical comparison such as height weight color of hair and eyes finger prints ability to taste phenylthiocarbamide funneling the tongue, the type of placenta and membranes birth weight and the nature of congenital defects if any In recent years detailed blood grouping of twins and their parents was carried out routinely for the following antigens A, B, C D, E c e M N S s P and in some cases grouping for Kell Lewis and Duffy was done We are indebted to Dr Fred H Allen Jr, of the Blood Grouping Laboratory Boston for carrying out these blood tests which have greatly increased our confidence in the zygosity determinations We are grateful also to the many doctors near and far who have referred epileptic twin pairs to us for study

VALIDITY OF THE SAMPLE

The ideal application of the twin method in medical genetics requires the random collection of a large number of individuals with a given disease followed by inquiry as to how many of them are twins The twin pairs are then studied in detail to determine the percentage of concordance for various aspects of the disease

This method was followed in the main in our study in that over two thirds of the sample consisted of clinic and private patients seen on routine referral without reference to twinning However we accepted for study any twin pair if one or both members had a history of seizures The sample consequently may include a number of twins who were sent because the referring physician knew of our special interest in twins Possibly he would consider a monozygotic or concordant pair more interesting and fail to send an equally important dizygotic or discordant pair Our data disclose that

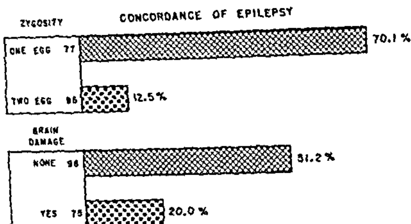


Fig 56 Concordance of a history of epilepsy in 173 twin pairs with respect to zygosity and brain damage prior to seizures Numbers of twin pairs in this and the next three figures appear at the base of the bars (or columns) and the percentage of concordance at the top The numbers concordant (from top to bottom) are 54 12 50 and 15

Conrad (10) with 157 pairs The former drew material from institutions in America, the latter from the entire hospital population of Germany " Neither had the advantage of blood typing or the electroencephalogram Also, the selection with respect to zygosity was unusual Of the combined 264 twin pairs, 20 per cent were monozygotic against 25–33 per cent for all twin births and 44 5 per cent for our present series In spite of these differences there is surprising agreement between these 20 year old reports and our own with respect to concordance of epilepsy in monozygotic pairs, namely, 70 per cent concordance Among dizygotic pairs, however, wide differences were reported, Rosanoff, 24 per cent, Conrad, 3 per cent and ours, 12.5 per cent

an

20 ... of the 42 symptomatic cases, 2 4 per cent (against our 51 2 and 20 per cent respectively as shown in the lower half of figure 56).

In figure 57 the influence of zygosity and of brain damage are dealt with separately The two upper bars represent twin pairs without acquired brain damage The topmost bar is for one-egg twins Concordance in these 51 pairs is 88 2 per cent Among nine twin pairs with ... in defect (the ...

appa ... 2 others, twin ... 7 two-egg ... per cent

The two bottom bars represent twin pairs with an acquired brain abnormality of the propositus Of 26 one-egg pairs the concordance is 34 6

Furthermore the sex ratio among dizygotic propositi does not differ significantly from that found in their twins (.10 > P > .05). In a monograph on psychotic and neurotic illnesses in twins Slater (8) has criticized our data because they were apparently obtained in the course of ordinary clinical work and were not found through a systematic survey. The bias introduced in sampling was discussed above. It is interesting that Slater's more elaborately collected series also had a significant excess of female propositi, and his sample showed a significant excess of dizygotic pairs whereas ours showed an excess of monozygotic pairs. The European MZ rate of 0.25 (19) was used for evaluation of his sample and the American MZ rate of 0.33 for our twins (11). The differences may reflect intrinsic variations in the distributions of the diseases by sex and type of twin rather than differences in the methods of sampling. The reduced viability of males results in a male female ratio of 124:100 in still born twins and a male female ratio of 128:100 in twin deaths during the first year of life. Possibly because of this differential viability the loss of males in twin births is excessive, and hence fewer pairs containing males would come to our attention. This is in keeping with our findings of a relative excess of monozygotic female pairs and a relative deficit of male co-twins among dizygotic female propositi. *Since the study began six males and three females have died.*

TWIN COMPARISONS

Twins are divided into three classes with respect first to the zygosity of twins, second to prior brain damage, and third as to whether seizures had been multiple and chronic or only febrile or confined to one or two. We have observed the involvement of both co-twins with respect to four conditions: first, epilepsy; second, the type of seizure; third, the brain wave pattern; and fourth, the I.Q. With respect to the epilepsy the distribution of the three classes is displayed in table 26.

CONCORDANCE IN EPILEPSY

The two uppermost bars of figure 56 refer to zygosity. The concordance of epilepsy among 77 monozygotic pairs is 70.1 per cent and among 96 dizygotic concordance is 12.5 per cent. The two lower bars refer to brain damage. *The concordance among 98 pairs without antecedent brain damage* is 51.2 per cent and among 75 pairs with damage it is 20 per cent. In this comparison the spread between groups on the basis of zygosity is more than twice the spread on the basis of an acquired brain lesion.

Several authors have given interesting case reports of one or a few epileptic twins, but only two reports have dealt with a large number of cases. These are by Rosanoff, Handy and Rosanoff (9) with 107 pairs and

TABLE 26

Data concerning 173 twin pairs with reference to presence and chronicity of seizures, zygosity, and antecedent brain damage

		Concordant				Discordant			Total both groups	Per cent, all twins
		Both chronic	One chronic One transient	Both transient	Total	One chronic One free	One transient One free	Total		
One egg pairs	Brain intact									
	No	31	4	10	45	5	1	6	51	
	%	60.8	7.84	19.6	88.2	9.80	1.96	11.8	100	29.5
	Brain lesion									
	No	4	5	0	9	17	0	17	26	
	%	15.4	19.2	0	34.6	65.4	0	65.4	100	15.0
	Total									
	No	35	9	10	54	22	1	23	77	
	%	45.5	11.7	13.0	70.1	28.6	1.30	29.9	100	44.5
Two egg pairs	Brain intact									
	No	2	3	1	6	37	4	41	47	
	%	4.26	6.38	2.13	12.8	78.7	8.51	87.2	100	27.2
	Brain lesion									
	No	4	2	0	6	43	0	43	49	
	%	8.16	4.08	0	12.2	87.8	0	87.8	100	28.3
	Total									
	No	6	5	1	12	80	4	84	96	
	%	6.25	5.21	1.04	12.5	83.3	4.17	87.5	100	55.5
All twin pairs	Brain intact									
	No	33	7	11	51	42	5	47	98	
	%	33.7	7.14	11.2	52.0	42.9	5.1	48.0	100	56.6
	Brain lesion									
	No	8	7	0	15	60	0	60	75	
	%	10.7	9.33	0	20.0	80.0	0	80.0	100	43.4
	Total									
	No	41	14	11	66	102	5	107	173	
	%	23.7	8.09	6.36	38.[illegible]	58.9	2.89	61.8	100	100.0

Mabel and Lulu Cla are 24 years old, reported by Little and Weaver (6). The paternal grandfather and a paternal uncle had had chronic epilepsy. The child of Mabel, the patient, has petit mal. At the birth of the twins the placenta and membranes were single; both weighed six and a half pounds. A pigmented mole was on opposite cheeks. Mabel is left handed, parts her hair on the right and is right eye dominant, whereas Lulu is the opposite except for having a dominant right eye. The right ear of one twin corresponds with the left ear of the other. The E.E.G.'s are similar and mildly abnormal because of paroxysmal eight per second waves in the parietal leads and 15 per second activity in all leads but especially in the right occipital of both. Mabel's abnormality is the greater.

A first convulsion began in Mabel at the age of 20, being generalized, tonic-clonic and

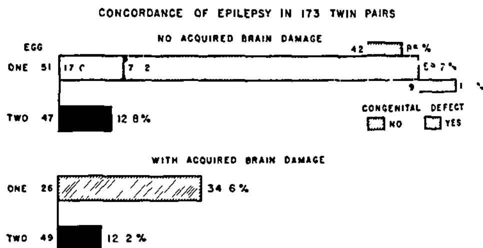


Fig 57 Concordance of epilepsy in 173 twin pairs with reference to zygosity in groups without and with brain damage prior to epilepsy The numbers concordant for the four bars are 45, 6, 9 and 6 Data given in the top bar is divided in nine pairs with congenital brain defect all concordant and 42 pairs 36 concordant without evidence of congenital brain defect

per cent. Among 49 two egg pairs, concordance is 12.2 per cent. As in the previous figure, the spread between degree of concordance on the basis of zygosity is more than twice the spread on the basis of an acquired lesion. The concordance of 88 per cent for monozygotic undamaged twins was almost the same as Conrad's, although his group numbered only 22 against our 51. Concordance of his other subgroups was much lower than ours. Perhaps co twins who had only transient or febrile seizures in early life were not classified as epileptic by Conrad.

The data consolidated in figures 56 and 57 appear in more detail in table 26.

Twin pairs that do not align themselves with the majority groups deserve special scrutiny. This involves, first, the six (out of 51) monozygotic uninjured *pairs in which only one co twin has a history of seizures and second* the six (out of 47) dizygotic uninjured pairs in which both co twins have such a history. The value of continued search for pertinent evidence and of re examinations of the twin pairs is illustrated by comparison with the report made by W. L. (1) three years ago. Of the 12 twin pairs which then were not in agreement with the expected concordance or discordance, six are eliminated from the present report. The displacements have not been due to a change in the seizure state but to reappraisal of zygosity or of acquired brain damage. Because of the youth of some twins and the short duration of the seizure history, present discordance may in time become concordance. This would apply to both one and two egg twin pairs.

years. Carol has been symptom free. Her E E G on repeated trials was normal until a record ing during sleep revealed spike-wave discharges. Karen's I Q at the age of seven years, was 98, Carol's, 95

Following are the six twin pairs, all dizygotic, which violate the expected by being concordant with respect to epilepsy

Lillian and Lorraine Cri are 18 years of age, one with transient, the other with chronic epilepsy. Their prenatal period was complicated by the mother's mild toxemia. At the age of two Lillian had a series of febrile convulsions over a 24 hour period. Four years ago at the age of 14 Lorraine began to have nocturnal convulsions. These have recurred four to ten times a year especially at the time of some infection. The most recent E E G's displayed for Lillian generalized high voltage spike discharges in the waking and atypical frontal spike discharges in the sleeping record. Lorraine's record had similar but exaggerated abnormalities. The tracings were unusually alike for an undoubted dizygotic pair. Lillian's I Q was 90, Lorraine's 100

Anthony and Patricia D Ag are nine years of age both with a history of febrile convulsions [illegible]

[illegible] and a half. Patricia had two febrile convulsions when an infant. The first of three E E G's displayed for Anthony fast spike wave formations on overventilation and for Patricia only a big buildup. Anthony's I Q was 83, Patricia's 89

Allen and Jane Fle four and a half years of age are patients at the Monson State Hospital, Dr Roger Osterheld superintendent. A great aunt had epilepsy. The twins were eight weeks premature weight three pounds 13¼ ounces and four pounds three ounces. Mental and physical retardation was noted after a few months. Tonic convulsions began in both twins in the first year. Evidence of severe congenital defect of the brain resulted in institutionalization

Phillip and Joan Gar are nine years of age both with a history of febrile convulsions. A paternal aunt and a maternal uncle had seizures in infancy, the latter dying at 11 months. Another maternal aunt had severe fainting episodes. The twins were born after a 60 hour labor. Phillip had a first febrile convulsion at 16 months and a total of six or eight. Joan's first was at 22 months with a total of about 15. Phillip's E E G was normal, Joan's had many slow waves. The boy's I Q was 90 three points above his sister's

Floyd and Lloyd Sm aged 16 years were examined by Dr Ruth Baldwin of Baltimore. Floyd's epilepsy is chronic, Lloyd's transient. Floyd ha[illegible]
Lloyd [illegible]
a g[illegible]
two [illegible]
has [illegible] slowing. Lloyd's has paroxysmal, high voltage slowing [illegible] motor seizures. The E E G

Lucia and Grace Tid are 16 years of age. The father fainted several times [illegible] once. Migraine was present in the mother, her [illegible] paternal uncles. At three years Lucia began to [illegible] several times daily but increasing in frequenc[illegible] convulsion. Both types of seizures have contin[illegible] under treatment with greatly reduced frequency. Grace's episodes probably psychomotor in type also began at three years but after two or three years she developed automatisms which have continued. Lucia's E E G had paroxysmal slow waves and two per second spike wave discharges more prominent in leads from the right. Grace's record on the other hand showed only minimal abnormality of

lasting 45 minutes. Attacks have *numbered approximately 15 but have been absent following* the prescription of Dilantin Lulu has been seizure free

Joseph and James Fee are 40 years of age As a boy Joseph was rendered unconscious by a blow on the head The twins have been followed clinically and electrographically for the past 15 years Joseph at one time experienced an hysterical hemiparesis Since about the age of 18 he has had many inadequately *described periods of unconsciousness* While serving an eight year prison sentence for impregnating a consenting girl under the age of consent although his twin was involved also, Joseph has had inadequate medication and frequent convulsions and psychotic outbursts the latter probably psychomotor seizures Both twins have migraine The I Q of Joseph at 120 is two points above that of James The E E G 's of both were considered normal until a sleep recording of Joseph disclosed slow spikes in the temporal areas James also is neurotic A history of what might be automatisms is too vague for identification

Robert and Richard Rea , referred by Dr Madeline Brown when last seen were 14 years of age Robert had experienced perhaps a dozen tonic convulsions and some periods of amnesia in the past four years His I Q at 102 was three points above his brother's who had had no seizures The E E G 's were normal and the same except that Robert s had a paroxysmal, big buildup with hyperpnea

James and Joseph Whi aged four were examined by Dr Ruth W Baldwin of Baltimore who supplied the needed information The mother had childhood convulsions and now has migraine One of her five children had febrile convulsions The labor lasted for 10 days with intermittent bleeding James was second born breech presentation He had experienced one seizure a month before his first visit He fell to the floor was unconscious for several minutes his face very blue He was confused afterwards and did not seem himself for several days The E E G 's of both boys were considered abnormal because of frequent paroxysms of high voltage four per second waves and persistence of a big buildup after cessation of hyperpnea

Jane and Elaine Wil are seven and a half years of age The father had fainting spells' in childhood and at 27 years had a tonic clonic convulsion following a venous puncture Of his seven siblings two had febrile convulsions and a third fainting spells A niece of the twins mother had convulsions to the age of six The mother and also her mother and sister have migraine The pregnancy was complicated by toxemia with albuminuria with weight increasing from 97 to 162 pounds Following delivery the mother had a series of perhaps 15 convulsions Placenta and membranes were single Jane the patient who was second born offered the most difficulty Her seizures autonomic in nature began at the age of five There was nausea and vomiting elevation of arms and eyeballs and unconsciousness for a few seconds If standing she would fall be pallid briefly unconscious and for an hour would have photophobia and sometimes headache There might be only nausea and abdominal pain After a year, frequency of attacks increased to two a month and consisted of a piercing cry rapid breathing rigidity pallor and gagging or vomiting Such attacks might occur in sleep Under [illegible] 18 [illegible] Elaine like Jane is subject to motion [illegible] vomiting but no discrete seizures [illegible] d excessive buildup on hyperpnea

Elaine's first E E G also slow was the more abnormal because of spike discharges in the left temporal lead The father's record displayed slight slowness The mother's is more abnormal because of slowing and six per second positive spikes Jane's I Q of 99 was three points above Elaine's

Karen and Carol Yon are now 15 years of age A maternal cousin has epilepsy Karen at the age of six began to have petite absence Attacks recurred *dozens of times daily the diagnosis* being confirmed by the E E G They disappeared with persistent use of trimethadione (Tridione), and they, as well as the fast spike-wave discharge, have been absent for seven

twins a total of 241 times (more than one type is represented in 69 pairs) The average concordance of all types is 80 8 per cent for the A group and 13 9 per cent for the B a ratio of more than five to one (not charted)

The last two pairs of columns demonstrate that concordance extends even to combinations of seizure types Indeed, when one co twin has both grand and petit mal the concordance is 76 9 per cent in group A and 7 7 per cent in group B In a large non twin series, patients with a history of both grand and petit mal had the most epileptic relatives (7) The low concordance of combined grand mal and psychomotor seizures (last pair), 44 4 per cent in group A and 6 6 per cent in group B, reflects the greater pathologic abnormality involved

CONCORDANCE OF ELECTRICAL PATTERNS

Early in their studies of the electroencephalogram, Lennox and the Gibbses called epilepsy a symptomatic paroxysmal, cerebral dysrhythmia In 1939 and again in 1940 they (12, 13) pointed to its value in the study of heredity After examining 71 non-epileptic twins, they (14), in 1945 announced that the brain wave pattern is an hereditary trait If these conclusions are correct the concordance of electroencephalographic discharges not due to some acquired condition, should exceed the con-

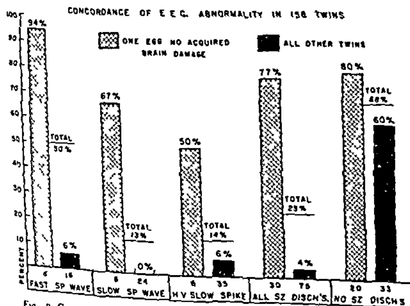


Fig 7 Concordance of EEG abnormality in 158 twins The hatched columns are for Group A the solid columns for Group B The numbers concordant for the columns left to right are 15 1 40 4 2 23 3 16 20

background frequencies Although there is concordance for epilepsy the clinical seizures and the E E G patterns are discordant

CONCORDANCE OF SEIZURE TYPES

Does heredity determine simply the presence or absence of epilepsy in any form, or does it determine the type of seizure? In figure 58 twins are divided into two groups, first (group A) are the monozygotic twins without acquired brain damage prior to the first seizure (the striped columns) Second (group B) are all other twins (black columns of the chart)

There are 144 pairs with a history of grand mal in one or both Grand mal occurs in both of the co twins in 86 4 per cent of those in group A but in only 17 per cent of those in group B Corresponding percentages for 42 pairs with petit mal are 83 3 per cent and 8 3 per cent and for 55 with psychomotor seizures 44 4 and 13 6 per cent The role of heredity appears to decrease progressively in the three groups petit mal grand mal and psychomotor Simple petit mal (petite absence) is less likely than other types to have a background of neuropathologic lesion The three separate seizure types—grand mal petit mal psychomotor—appear in the series of

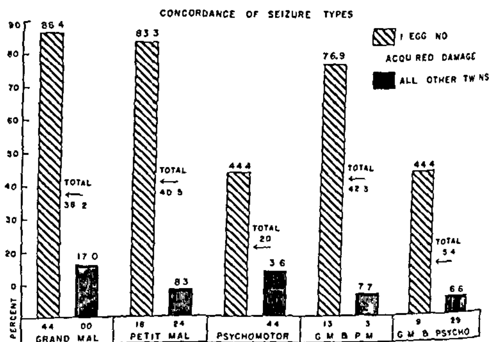


Fig 58 Concordance of seizure types C l s th l g al stripes are f r Group A s are f r all r gl t are 34 co c rdance

respectively In contrast with the three per second spike-wave discharges, these forms are often associated with pathologic lesions

For all seizure discharges (the fourth pair of columns) the concordance for A group is 77 per cent and for the B group is 4 per cent The last two columns represent E E G records which were normal or showed only an abnormally fast or slow dominant background rhythm Concordance of these non specific and minor abnormalities is large and does not differ much for groups A and B

The strong evidence of heredity or lack of it for certain brain wave patterns is in spite of the handicap of time The history of epilepsy and of various types of seizures covers years where as electroencephalographic recordings extend for minutes only Also seizures experienced in the past do not diminish in number whereas the present electroencephalogram may contain fewer abnormalities than when seizures were active the spike wave discharge of petit mal especially tends to vanish as the person becomes adult

LIKENESS OF DETAILS OF ELECTRICAL PATTERNS

One more especially convincing point remains In monozygotic twins without evidence of brain damage the three per second spike wave patterns are *identical* in many of their smaller details such as distribution through the various leads the relative amplitude of spikes and waves and the con

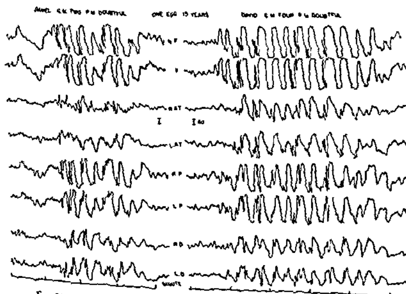


Fig 81 EEGs of Daniel and David Cay (From Lennox 1 by permission)

cordance of epilepsy in general and of any specific form of epilepsy in particular.

Paroxysmal bursts of high voltage waves abnormally fast or slow (seizure discharges) occurred in one or both of 105 twin pairs. In figure 59 these are divided into groups A and B as previously. The screened columns represent the 30 monozygotic twins without acquired brain damage, the black columns are all other twins, 75 in number.

The two columns on the left represent the electroencephalograms of 32 twin pairs, one or both of the co-twins having a three per second spike wave discharge which we regard as diagnostic of petit mal epilepsy. The concordance is 94 per cent in group A and only 6 per cent in group B. The number of twin pairs of group A with other types of seizure discharge is small, only six with slow spike wave and eight with high voltage slow waves or spikes. Hence concordances shown for these patterns in figure 59 must be interpreted with caution. The number of persons in group B is adequate. If these two groups are combined the concordance is 13 and 14 per cent for the slow spike wave and for slow waves or spike discharges

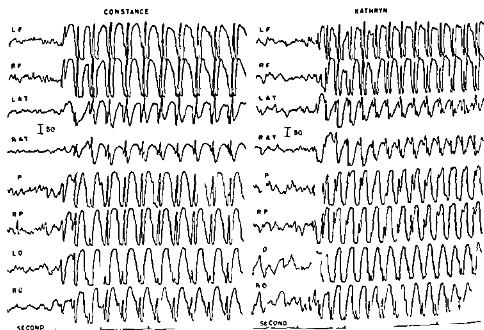


Fig 60 EEGs of Constance and Kathryn McN. In this and succeeding figures the letters refer to the placement of electrodes: F, frontal; T, temporal; AT, anterior temporal; P, parietal; and O, occipital; either L (left) or R (right). Monopolar recording is used. The signal at the left measures 50 microvolts and the line at the bottom seconds. (From Lennox, by permission)

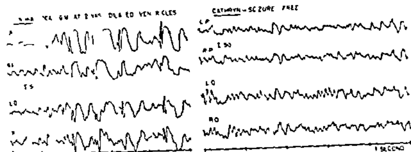


Fig 63 EEGs of Cynthia and Cathryn Mar

and amnesia some lasting an hour or more. Observed closely he has been seen to have momentary staring which might be either petit mal or psychomotor episodes. Hubert's waking EEG was not distinctive but during sleep there were brief, generalized discharges of high voltage spikes and high voltage slow waves. Such a discharge is equivocal, not presenting distinctive alternate spike wave formations. Whatever their interpretation, similar discharges occur in the waking record of the normal twin Herbert. He did not sleep but had imbibed freely of beer some 12 hours before the recording. These twins also illustrate the failure of chronic epilepsy to influence a patient's I. Q. Scores from Wechsler Bellevue testing (verbal, performance and the full score) were as follows: Herbert 99, 92 and 96, Hubert the patient, 99, 93 and 96.

In group B there were 24 twins with a slow spike wave discharge in the E E G of at least one co twin. Among these, four monozygotic twins had a history of brain damage in one (the epileptic) co twin. The following two cases represent these four.

Figure 63 represents tracings from the records of Cynthia and Cathryn Mar, nine year old monozygotic twins. The brain of Cynthia probably was injured at birth. Focal right sided convulsive seizures were frequent, the pneumogram displayed dilated ventricles and her I. Q. was 70, 22 points below her unaffected sister. The spike wave discharges seen especially in the left parietal and occipital leads are of the slow, irregular variety, whereas the record of her unaffected twin is relatively normal.

Figure 64 compares tracings from the occipital leads of Kent and Kerry Tay, monozygotic seven year old twins. The mother has migraine. Kent has cerebral palsy and a left hemiparesis noted at 10 months. When four years of age he had three prolonged febrile convulsions. For many years he has been subject a number of times a month to minor seizures in which he stops, looks frightened, is pale and gulps repeatedly. He retains consciousness but after about a minute symptoms end and the boy lies down and sleeps soundly for an hour or so. He is a severe behavior problem. His I. Q. is 75, which is 22 points below that of his unaffected twin. During sleep there were many sharp triphasic spikes in the right occipital lead, some followed by a hump. Kerry's waking record showed only relative inactivity of the left occipital lead.

GENETIC MECHANISMS

Data from monozygotic twins helps us to establish the degree of inheritability of epilepsy, and the percentage concordance in monozygotic twins is, for practical purposes, equal to the penetrance of the gene or genes, but

tour of the waves The point can be made clear only by viewing samples of the tracings We reproduce short sections of records of five monozygotic twins, three with three per second and two with two per second spike-wave discharges

The three with fast spike-wave discharges represent the 15 (out of 16) twins in which there was concordance with respect to the principal E E G abnormality.

Figure 60 represents the dysrhythmia that attends the onset of petite absence in monozygotic 11 year old twins, Constance and Kathryn McN Frequent daily attacks had been present for three years Family and personal histories were unrevealing On Tridione medication clinical seizures disappeared but spike wave discharges continued, necessitating the resumption of medication Their I Q 's were Constance—verbal, 101, performance, 119 and full score, 110, Kathryn—verbal, 101, performance, 111 and full score, 106

Figure 61 displays spike wave seizure discharges in the E E G 's of both Daniel and David Cav , monozygotic 15 year old twins At this time Daniel had had two and David, four convulsions A definite history of petite absence (discrete blackouts of consciousness) could not be obtained The boys confessed to brief periods of dizziness Probably these coincided with more prolonged periods of spike wave discharges than those that appear in the figure Their I Q 's were Daniel—verbal 85, performance, 77 and full score, 80, David—verbal 90, performance, 78 and full score, 80

Figure 62 contains seizure discharge from the records of monozygotic twins, Herbert and Hubert Bur , aged 28 years Herbert (left hand panel) has had only two convulsive seizures at the age of eight and eighteen Hubert beginning at the age of 10, had had approximately 300 grand mal and 100 psychomotor seizures, the latter characterized by periods of confusion

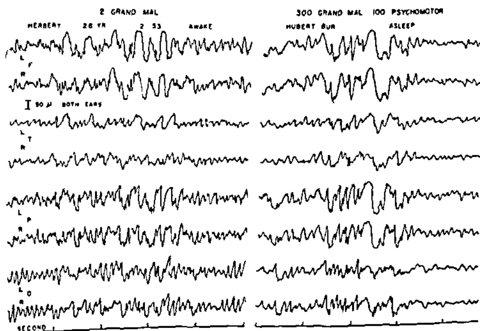


Fig 62 E E G's of Hubert and Herbert Bur

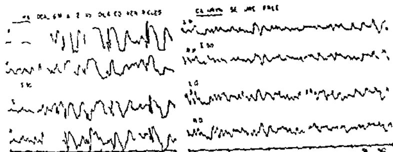


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and amnesia some lasting an hour or more Observed closely he has been seen to have momentary staring which might be either petit mal or psychomotor episodes Hubert's waking EEG was not distinctive but during sleep there were brief, generalized discharges of high voltage spikes and high voltage slow waves Such a discharge is equivocal not presenting distinctive alternate spike-wave formations Whatever their interpretation similar discharges occur in the waking record of the normal twin Herbert He did not sleep but had been deprived of sleep some 12 hours before the recording These twins also illustrate the failure of minor epilepsy to influence a patient's I Q Scores from Wechsler Bellevue testing (verbal performance and the full score) were as follows Herbert 99 92 and 96 Hubert the patient 99 93 and 96

In group B there were 24 twins with a slow spike wave discharge in the EEG of at least one co twin Among these four monozygotic twins had a history of brain damage in one (the epileptic) co twin The following two cases represent these four

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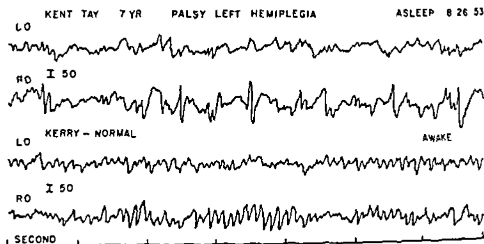


Fig. 64. EEGs of Kent and Kerry Tay

they tell us nothing about the mechanism of its inheritance. On the other hand, the frequency of concordant dizygotic twin pairs can be of some use in this respect. In a trait which depends on either a single dominant gene *A* or a pair of recessive genes *aa*, the discordant pairs must result from the mating of *Aaxaa* and/or *Aax Aa*. This may be simplified further for a disease such as epilepsy with a disease rate of one half to one per cent. Among dizygotic twins, in the case of a rare dominant gene *A*, practically all the discordant pairs will result from *Aaxaa* matings. In the case of a rare recessive gene *a*, *Aax Aa* is the only mating of importance in producing discordant pairs. Rife (15) has shown that for twins randomly selected and subsequently studied for a given trait we should expect concordance in dizygotic pairs to have maximum of 33 per cent for a simple dominant and a maximum 14.3 per cent for a simple recessive. His technique cannot be applied to our data since we always knew one twin was epileptic.

In our case, with full expression, we expect maximum concordance of 50 per cent in dizygotic twins for simple dominant and 25 per cent for simple recessive inheritance. These maximum values will be reduced by such factors as incomplete penetrance and variability of age of onset. For epilepsy, using the 70 per cent concordance found in monozygotic twins as a measure of penetrance, the expected concordance in dizygotic twins would be about 35 per cent for a dominant and about 17 per cent for a recessive gene. While the observed concordance of 12.5 per cent fits the hypothesis of simple recessive inheritance better than simple dominant, it does not allow us to rule out alternative genetic hypotheses.

The intra-uterine situation of twins is very different from that of single births. In the general population only about one person in 50 has experi-

enced this special prenatal environment Hence unqualified statements about the degree of heritability of a trait cannot be made from twin data alone These suggest that paranatal environmental conditions, to which dizygotic twins are exposed greatly increase the tendency to epilepsy Some of the factors which may increase the concordance in dizygotic pairs above that of siblings are the increased incidence of toxemia prematurity, bleeding breech presentation and other obstetrical complications which are all more common in twin births In prenatal life a serious insult might be expected to affect both twins more frequently than a recurrent insult in the same mother in two pregnancies that result in single births

Further elaboration of the mechanism awaits detailed family studies of larger numbers of patients The present study is being extended to include the parents and siblings of the twins with recording of seizure history, brain wave patterns, blood groups and certain other physical characteristics in which the mode of inheritance is straight forward The resulting data should permit a search for genetic linkages

THE ROLE OF NATURE AND NURTURE IN MENTALITY

Mental deterioration is a prime characteristic of epilepsy General belief in this old time statement underlies much of the social stigma and the discriminatory laws that plague the epileptic Laws against marriage presuppose transmission not only of epilepsy but also of mental defect What are the facts?

We have secured intelligence tests of 130 of the twin pairs Individual scores range from 20 to 140 In the two figures that follow the scores of co twins of each pair are plotted as a single point If scores of the two co twins are the same the point will fall on the diagonal Value for the normal or least affected co twin is plotted on the abscissa Three complicated cases are not charted

Figure 65 is of 60 monozygotic twin pairs The left half is of 36 without brain damage Symbols cluster close to the diagonal When both co twins are chronically affected as shown by the dots the average values (indicated by the lower star) are 97 5 ± 4 2 and 96 9 ± 4 4 with a correlation coefficient of 89 In nine pairs shown by crosses one co twin has chronic epilepsy and the other has either been seizure free or has had no more than two seizures The averages for this group (indicated by the upper star) are 103 ± 3 9 and 104 ± 4 6 with a correlation coefficient of 94

The right half displays scores of 24 pairs in which one co twin had experienced brain damage The average score is 75 ± 5 1 for the one with the pathologic brain and 99 ± 3 1 for the unaffected a spread of 24 points The correlation coefficient is 47

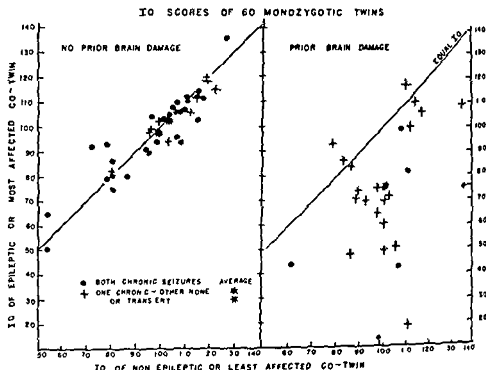


Fig 65 I Q scores of 60 monozygotic twins In this chart the dots represent twins in which both have chronic epilepsy The crosses are for those in which one co twin either has only transient or no seizures In the left hand panel the large circles indicate the average of each of these two groups the uppermost being for twins when both co twins have chronic epilepsy The diagonal represents an equality of the two twins The I Q of the epileptic or the more affected of the co twins is placed on the ordinate scale The star dots and the arrows pointing from the side indicate the average values for the cases in each panel

Figure 66 contains the I Q scores of 67 dizygotic pairs The left half is of 33 dizygotic pairs without acquired brain damage There is wide scattering of symbols, but the average I Q value denoted by the star, is close to the diagonal The average I Q of the most affected is 89 ± 4 9 and of the least affected, 92 ± 6 2—a spread of three points The correlation coefficient for the group is 65

The right half is for pairs in which one of the co twins has suffered brain damage Scattering is more widespread and the joint average I Q is far below the diagonal, with the most affected scoring 71 ± 5 1 and the least affected, 97 ± 3 3 This denotes a spread of 25 points in favor of the undamaged co twin The correlation coefficient is 39

A rough measure of the degree to which heredity is responsible for the variations in intelligence between twins can be calculated from the correlation coefficients as Holzinger's index (16) This is (*h*), which measures the proportion of variation due to heredity in a given trait, where *rmz* is the

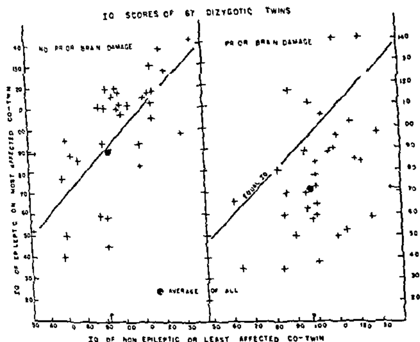


Fig 66 I. Q scores of 67 dizygotic twins the left and right hand portions for those respectively without and with prior history of brain damage The crosses spot the I Q scores of both co-twins In each case only one co-twin has chronic seizures

intra-class correlation coefficient of monozygotic and r_{DZ} of dizygotic twins—$h = \dfrac{r_{MZ} - r_{DZ}}{1 - r_{DZ}}$

For the twins without brain damage—$h = .82 - .646 = \dfrac{.174}{.354} = .49$

For the twins with brain damage—$h = \dfrac{.467 - .393}{1 - .393} = \dfrac{.074}{.607} = .12$

Thus about half (.49) of the variation of I Q in the undamaged group is due to heredity compared with one eighth (.12) in the group with brain damage

To examine the relative effect of heredity and of seizures on intelligence, we may calculate h for the two groups of twins without antecedent brain damage The first group in which both co twins have chronic seizures, is too small to make calculation of the index worth while As an alternative, we can take the results secured by those who have studied normal twins and compare these with our second group in which one co twin has chronic seizures and the other is seizure free or has had no more than two

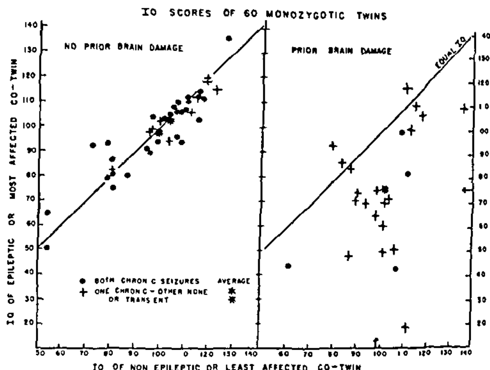


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The right half is for pairs in which one of the co-twins has suffered brain damage. Scattering is more widespread and the joint average I. Q. is far below the diagonal, with the most affected scoring 71 ± 5.1 and the least affected, 97 ± 3.3. This denotes a spread of 25 points in favor of the undamaged co-twin. The correlation coefficient is .39.

A rough measure of the degree to which heredity is responsible for the variations in intelligence between twins can be calculated from the correlation coefficients as Holzinger's index (16). This is (*h*), which measures the proportion of variation due to heredity in a given trait, where r_{MZ} is the

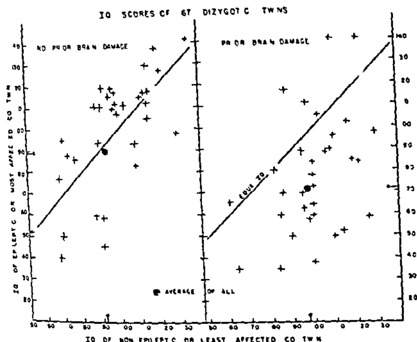


Fig 67 I Q scores of 67 dizygotic twins the left and right hand portions for those respectively without and with prior history of brain damage The crosses spot the I Q scores of both co-twins. In each case only one co-twin has chronic seizures

intra-class correlation coefficient of monozygotic and r_{DZ} of dizygotic twins—$h = \frac{r_{MZ} - r_{DZ}}{1 - r_{DZ}}$

For the twins without brain damage—$h = 82 - 646 = \frac{174}{354} = 49$

For the twins with brain damage—$h = \frac{467 - 393}{1 - 393} = \frac{074}{607} = 12$

Thus about half (49) of the variation of I Q in the undamaged group is due to heredity compared with one eighth (12) in the group with brain damage

To examine the relative effect of heredity and of seizures on intelligence we may calculate *h* for the two groups of twins without antecedent brain damage The first group in which both co-twins have chronic seizures is too small to make calculation of the index worth while As an alternative we can take the results secured by those who have studied normal twins and compare these with our second group in which one co-twin has chronic seizures and the other is seizure free or has had no more than two

$$\text{For this group } h = \frac{937 - 765}{1 - 765} = \frac{172}{235} = 74$$

This value of 74 approximates the value 67 obtained by Wingfield (17) for the Holzinger index. Newman et al. (18) obtained a value of 68 for the Binet test. This means that in our pairs with only one co-twin chronically affected as in normal twins nature is twice as powerful as nurture. In other words, *in the absence of brain damage epilepsy does not affect mentality adversely.*

We conclude, therefore, that the mental state of persons with metabolic epilepsy, as with persons in general, depends mainly on their heredity. Whether or not they have seizures is relatively unimportant if complications such as a cerebral thrombosis or brain trauma from a fall are absent. In acquired (symptomatic) epilepsy, on the other hand, brain damage is mainly responsible for both epilepsy and mental decay. Again the resultant effect of genetic and acquired forces determines both epilepsy and mentality.

Our present contribution suffers from the small numbers involved. The effective application of the twin method to problems of human genetics requires the development of systems for routine recording of twin index cases in hospitals and departments of vital statistics. An association such as this might sponsor such a register of epileptic twins. Failing this, we *invite the cooperation of members who encounter twins in their practice.*

Results of studies such as this when applied to questions of marriage and children must be viewed in proper relationship and perspective. For example, how does the degree of inheritance compare with that in other illnesses? What other desirable traits may outweigh a tendency to seizures; what are the genetic traits of the partner in marriage; what is the possibility for preventing the conditions that activate an underlying tendency to seizures, and if epilepsy comes, what are the chances for control? As with other questions that involve *the epileptic, this one must be highly individualized.* Nature and nurture each varies in importance. Some epileptics should not procreate; others decidedly should.

CONCLUSION

With the aid of friendly referring doctors plus an offer of free examinations and treatment, we have studied 173 twin pairs subject to seizures. Among monozygotic twins without prior brain damage, the concordance *of epilepsy, both absolute and compared with other twins,* is high. This high concordance extends to the type of seizure and, more importantly and explicitly, to the three per second spike wave pattern of the electroencephalogram. The degree of concordance in dizygotic twins points to a simple recessive. Intelligence tests of 130 twin pairs indicate that intelligence, like epilepsy itself, depends on heredity or on brain damage, or

both but is not importantly affected by seizures Many considerations enter into the question of marriage We believe that most epileptics who wish to marry and rear children should be encouraged to do so

DISCUSSION

DR ARNOLD L GESELL [New Haven, Conn] I would like to add a brief comment This paper is a very impressive demonstration of the precision of the developmental mechanisms of behavior which operate in normal as well as in pathological conditions

In our studies of monozygotic twins we have been able to subject the patterns of normal behavior to minute analysis of cinema records And we have often found a remarkable identity in such characteristics as psycho-motor speed the ontogenetic timing of the extension of the index finger the patterns of stair climbing and of fine prehension in infant twins In one pair of twins of school age we even found detailed identities in the misspelling of words Deep seated mechanisms govern the correspondences in the developmental morphology of behavior in normal twins

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$$\text{For this group } h = \frac{937 - 765}{1 - 765} = \frac{172}{235} = 74$$

This value of 74 approximates the value, 67 obtained by Wingfield (17) for the Holzinger index Newman et al (18) obtained a value of 68 for the Binet test This means that in our pairs with only one co twin chronically affected, as in normal twins, nature is twice as powerful as nurture In other words, in the absence of brain damage epilepsy does not affect mentality adversely

We conclude, therefore, that the mental state of persons with metabolic epilepsy, as with persons in general depends mainly on their heredity *Whether or not they have seizures is relatively unimportant if complications* such as a cerebral thrombosis or brain trauma from a fall are absent In acquired (symptomatic) epilepsy, on the other hand, brain damage is mainly responsible for both epilepsy and mental decay Again the resultant effect of genetic and acquired forces determines both epilepsy and mentality

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were able to recall that a parent also had attacks of 'sick headache' of a similar nature Lennox contrasted this group of 425 headache patients with a control group of nurses, medical students, and miscellaneous patients, among whom 11 per cent were able to recall a parent with migraine headaches

INCIDENCE OF MIGRAINE HEADACHE

In the consideration of an hereditary trait, the incidence of the trait in the general population is of interest and significance In the present study it has not been attempted to collect new data on this aspect of migraine However Lennox (9) based on his own experience of finding an incidence of migraine of 5 4 per cent in his control group of 1000, and on the studies of Balyeat and Rinkel (1) who found the incidence of migraine in different social groups varying from 3 7 per cent to 13 5 per cent made a conservative estimate of 5 per cent as the incidence of migraine in the general population Weider et al (12) in a group of 10 000 young males found an incidence of 9 per cent of frequent severe incapacitating headaches Also in a study of 15 000 patients in general practice Grimes (7) found an incidence of 8 per cent of migraine headache whereas Fitz Hugh (3) in reviewing the private office records of 4 000 consecutive patients over 15 years, found an incidence of 22 per cent of migraine headaches

PURPOSE OF THIS STUDY

The hypothesis that migraine is not only familial but is also an inherited trait has been supported, and a definition of its mode of inheritance has been indicated by statistical analysis of family pedigrees obtained from 119 patients

BASIS OF SELECTION OF PATIENTS FOR STUDY

The patients selected for study had come to the New York Hospital complaining of severe headaches recurring usually over many years They were selected for this study on the basis of the following definition of migraine headache Pain was usually unilateral in onset sometimes becoming generalized before the end of the attack Attacks were from less than an hour to several days in duration The headache attacks were associated with anorexia nausea and vomiting as well as with photophobia and mood changes Some of the attacks were ushered in by scotomata hemianopia unilateral paresthesia or speech disorder Some attacks were accompanied by vertigo pallor excessive sweating and chilliness These and a host of other features did not all occur with each attack Some of the women patients had their headaches at the time of menstruation Furthermore in all instances the course of the headache was altered by ergot

CHAPTER XX

THE FAMILIAL OCCURRENCE OF MIGRAINE HEADACHE: A STUDY OF HEREDITY

HELEN GOODELL, RICHARD LEWONTIN, AND HAROLD G. WOLFF[1]

The patient with migraine headache commonly reports that some other member of his family has similar headaches. The *migraine syndrome* has long been considered familial, and some investigators have presented familial occurrences as evidence of its hereditary character. In 1873, Liveing (10) in his monograph on "megrim", commented on the frequent occurrence of migraine in the relatives of his "megrim" patients, and observed that this disorder was often transmitted from parent to child, especially from a parent to those children who in other respects resembled him. Christiansen (2) was of the opinion that migraine is a dominant hereditary factor, based on his observation of the very high percentage of his patients with severe migraine who had near relatives with migraine. Ulrich (11) studied 500 cases of migraine headache and believed they all inherited a migraine constitution, and that circumstances such as alcohol, infection, fatigue, worry and want do not cause migraine, but precipitate it in such patients. Fitz Hugh (3) suggested that migraine is a constitutional predisposition of the individual to react with headache to a variety of stimuli which, in the non-migrainous members of the population, produce no such comparable effect.

FAMILIAL OCCURRENCE OF MIGRAINE HEADACHE

Friedman (4) studied a large group of clinic patients with migraine headache, 65 per cent of whom gave a family history of migraine. Balyeat and Rinkel (1) stated that the factor of heredity in migraine was unquestioned, and presented four detailed family trees showing the occurrence of migraine in two and three generations. Graham (5), in a study of 467 patients with migraine headaches, reported that 80 per cent of them gave a history of having relatives with migraine among immediate family of siblings, parents, aunts, uncles and grandparents. Lennox (9) found 61 per cent of a group of 425 patients with migraine headache at the Boston City Hospital, who

[1] From the New York Hospital and the Departments of Medicine (Neurology) and Psychiatry, Cornell University Medical College, New York, and from the Department of Zoology and the Institute for the Study of Human Variation, Columbia University, New York.

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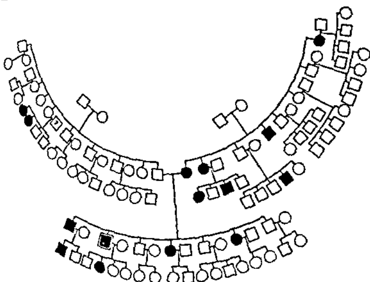


Fig 67 Family pedigree of a male patient showing migraine headache in 3 generations

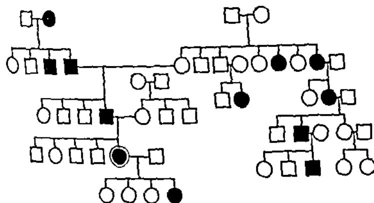


Fig 68 Family pedigree of a female patient showing migraine headache in 4 and 5 generations

means of amplifying and corroborating information given by questionnaire, and by letter A copy of the questionnaire is as follows

DATE
NAME

MIGRAINE HEADACHE QUESTIONNAIRE

Will you recall to the best of your ability any members of your family who have or have had migraine headaches? Please list *all* of your relatives indicating those who have had or have the headaches

amine tartrate, and a family history of similar attacks was obtained from 83 per cent of the 119 subjects (6, 13)

Because of their availability as residents of New York City and vicinity, 90 clinic patients of the New York Hospital were requested to come for an interview in regard to their migraine headaches Ten of the request letters were returned address unknown 8 patients could not come for an interview, to 4 letters there was no reply, and 3 patients who came for interview were discarded because they had no knowledge of their families Thus, 65 of the 119 patients studied had been treated for migraine headache during the past two years in an out patient clinic of the New York Hospital

There was another group of 80 private patients who had at some time during the previous 4 years consulted one of the authors (HGW) in regard to their migraine headaches Because the majority of this group lived at such a distance from New York that a personal interview did not seem feasible information about their relatives was requested by means of a mailed questionnaire, which was accompanied by an explanatory letter Fourteen of these were returned marked address unknown , and to 12 there were no replies In addition to answering the questionnaire 25 of these private patients came for personal interviews From the remaining 29 information was obtained from the questionnaire and letters

METHODS OF COLLECTING DATA

Each one of the group of 65 clinic patients was interviewed in person for the purpose of questioning him or her, about the occurrence of headaches similar to his or hers, in other members of the family Each patient was first asked the question Does anyone else in your family have migraine headaches similar to yours? He was then asked to describe the relative s headache or if he could not do this he was asked to get such a description from the relative himself or from another member of the family The number and sex of siblings and children of the patient and of his parents and grandparents (where possible) were recorded Each patient was urged to visit and to communicate by telephone and letter with any relative who might be able to extend or corroborate information about the occurrence of migraine in other members of the family The authors interviewed 34 relatives of this group of 65 clinic patients either in person or by telephone in order to amplify information given by patients

A family pedigree as illustrated in figures 67 and 68 was drawn for each patient

As mentioned above information about migraine headaches in the relatives of 54 private patients was obtained by means of a questionnaire and letters The personal interview with 25 of this group was a

equipment might give expression to headache in one environment and not in another. Also the mere fact of having one or both parents with migraine may be an environmental influence conducive to migraine in the offspring. No opportunity has yet offered to test the occurrence of migraine in such offspring reared by foster parents without migraine.

Furthermore, the method of obtaining information about the occurrence of migraine headache in other members of the family, by asking patients to recall such illness in relatives both temporally and spatially distant, may be seriously unreliable, especially since the complaint of pain in the head from a variety of causes can be elicited from approximately 65 per cent of the population. However, there is an immediate advantage in terms of the probable reliability of data obtained from persons with migraine headache. Such persons are usually characterized by their perfectionism, their excessive feelings of responsibility, and their need to perform with exactitude and meticulous attention to detail. (9, 11, 13)

DESCRIPTION OF DATA

Of the group of 119 propositi (i.e., patient informers) 48 were males, 71 were females. Twelve of the males and 2 of the females were physicians. All of the men were employed, and approximately half of the women. The remainder of the women reported themselves as housewives. Ages of the group ranged from 16 to 65 years, and were distributed as follows:

Age group	Number of patients
16 to 25	7
26 to 30	12
31 to 35	13
36 to 40	13
41 to 45	22
46 to 50	22
51 to 55	17
56 to 60	9
61 to 65	4

Sixty-one patients remembered having migraine headaches in childhood or in adolescence.

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...ution of relatives with migraine was as follows: 80 patients had no relatives with migraine; 66 patients had from 1 to 3 relatives with migraine; 22 patients had from 4 to 7 relatives with migraine and 11 patients had from 8 to 19 relatives with migraine. In the families in which these instances of migraine occurred there was a total of 832 offspring.

Mother		
Father		
Brothers	Total number	How many with migraine headaches?
Sisters	Total number	How many with migraine headaches?
Mother's mother		
Mother's father		
Mother's sisters	Total number	with migraine headaches?
Mother's brothers	Total number	with migraine headaches?
Father's mother		
Father's father		
Father's sisters	Total number	with migraine headaches?
Father's brothers	Total number	with migraine headaches?
Cousins on your mother's side	#	with migraine headaches?
Cousins of your father's side	#	with migraine headaches?
Your children		
Your spouse		

In addition, can you or your parents recall, or can you obtain information about migraine headaches occurring in great grandparents?

Whenever possible, information about the occurrence of migraine in the family of the patient's spouse was also obtained

These 119 patients gave evidence that they had made careful effort to verify their statements about their relatives having migraine headaches In 34 instances, as mentioned above, the authors were able to interview siblings, children, or parents of patients, either in person or by telephone to amplify the description of headaches, and make it certain that they actually had migraine headaches Many patients made visits and telephone calls or wrote letters of inquiry to relatives who lived at a distance It was thus that it was possible to obtain information, from surviving relatives' descriptions, of the occurrence of migraine headache in three, four and even five generations of a family One patient was in possession of the diary of her great grandmother, who had faithfully recorded her recurrent incapacitating migraine attacks There were 12 male and 2 female physicians in the group who took special care to verify the occurrence of migraine headaches in their relatives and to construct extensive family pedigrees One woman wrote to a surviving grandmother in Ireland whom she had never seen for information about her father's numerous siblings A male patient whose father had 10 siblings and mother 5, made many family visits, and carried on correspondence for several months with aunts, uncles, and cousins scattered from Maine to California, until he was satisfied that he had assembled a correct pedigree

COMMENT ON RELIABILITY

In dealing with these human clinical data it was recognized that genetic controls were lacking It was appreciated that an identical hereditary

Comment

Data showing the occurrence of migraine headaches in families for two three, or more generations have, to a number of investigators in the past strongly suggested the hereditary nature of the migraine trait. More suggestive evidence of the hereditary nature of the trait can be seen, however in the summarized data presented in table 28 especially because it is evident that the probability of having migraine headache in offspring increases with the number of parents affected. Therefore, in order to establish the significance of these data as regards the hereditary aspect of the migraine trait, genetic concepts of heredity and mode of inheritance have been applied.

APPLICATION OF GENETIC CONCEPTS AND MODE OF INHERITANCE

It was assumed that the trait of migraine headache was *not* inherited. A chi square test of homogeneity was applied to the differences between the actually observed and the theoretically expected frequencies of migraine in the 832 offspring in the families of the 119 propositi. This computation revealed a probability of less than one chance in a thousand that such deviations would occur if the assumption of no inheritance were true (see table 29). Therefore stated positively, it is highly probable that migraine is inherited. Furthermore it is reasonable to assume that migraine is due to a recessive gene whose penetrance is approximately 70 per cent. Penetrance indicates the ability of a gene to be sufficiently active in the development of an organism so as to show its effect in the final phenotype.

TABLE 29

Measure of inheritance

(Includes offspring where propositus is only affected person in family)

Migraine		No parent	One parent	Both parents	Totals
Offspring affected	Observed	76	222	45	343
	Expected	109	207	27	
	Difference	−33	+15	+18	
Offspring non-affected	Observed	189	280	20	489
	Expected	156	235	38	
	Difference	+33	−15	−18	
Totals		265	502	65	832

Chi square $= \Sigma \frac{(\text{Observed} - \text{Expected})^2}{\text{Expected}} = 39.35$ (with 2 D.F.) P = <0.001. Therefore the trait of migraine is inherited.

TABLE 27

Occurrence of migraine in generations of the pedigrees

Generations	Males	Females	Totals
1	9	15	24
2	20	23	43
3	13	27	40
4	4	5	9
5	2	1	3

There were reported to be relatives with migraine in as many as 5 generations of 3 of these families, in 4 generations of 9 families, in 3 generations in 40 families. A summary of the occurrence of migraine in the generations of the pedigrees is shown in *table 27*, and examples are illustrated in *figures* 67 and 68.

Figure 67 is the family pedigree of a male propositus, age 65, a physician who was able to verify to his satisfaction the diagnosis of migraine headaches in 14 of his relatives, distributed among 3 generations. Figure 68 is the pedigree of a female propositus, aged 42, who had 11 relatives with migraine, distributed among 5 generations.

From examination of figures 67 and 68, the number of offspring in families having members with migraine can be counted, and those offspring having parents with migraine can be counted separately from those whose parents do not have migraine; also, the total number of offspring having migraine can be counted. Such counts were made for each pedigree of the 119 propositi. Table 28 summarizes the incidence of migraine headaches among the 832 offspring in the families having members with migraine. Thus, among 265 of these offspring having neither parent with migraine, 76, or 28.6 per cent, had migraine; of 502 having one parent with migraine, 222, or 44.2 per cent, had migraine; and of the 65 offspring both of whose parents were affected, 45, or 69.2 per cent, had migraine headaches.

TABLE 28

Occurrence of migraine in the children of families having members with migraine

Children	Parents having migraine		
	No parent	One parent	Both parents
Total number of children	265	502	65
Number with migraine	76	222	45
Per cent with migraine	28.6	44.2	69.2

to assume correctly that the inheritance of the migraine headache trait is through a recessive gene with a penetrance of approximately 70 per cent.

DISCUSSION

DR. LAWRENCE H. S[illegible]YDER (Norman, Oklahoma): I would like to ask Miss Goodell if she considers migraine an allergic [illegible] and [illegible] whether any tests or searches for allergy in the other members of the family, especially [illegible] parents [illegible] migraine [illegible] did not have migraine, were made.

PRESIDENT HOOKER: We have a question from the floor from Dr. [illegible] of New York. Would Miss Goodell or Dr. Wolff indicate what features resulting in the migraine headache attack are inherited by the patient?

DR. HAROLD G. WOLFF (Closing): To deal with the question concerning allergy first. It does not happen to be our opinion that allergy is an important or necessarily a relevant factor [illegible] attacks and we have no data concerning the incidence of allergy in the families of headache patients.

The second question raised by Dr. [illegible] indicates quite rightly an uneasiness on the part of anyone to talk about heredity or the hereditary aspects of a pain. After all, what a pain represents is the result of noxious stimulation of some sensitive pain structure of the body, and in the case of migraine in the head, and therefore one is interested in knowing something about the mechanism or the relevant feature that gives rise to the disturbance.

We have discussed at this [illegible] three levels: first, in regard to the actual change in the body that is pertinent to the pain and that has become evident, and I think that most will agree that the fact that is relevant to the pain [illegible] the contracted state and dilatation of the cranial vasculature. There are a host of details [illegible] as to the exact vessels and the precise nature of the disturbance that gives rise to noxious stimulation, but it has something to do with the vasomotor state of these cranial vessels and perhaps also to the metabolic changes that go on in them during attacks. If we accept this as reasonably well established, we can analyze what the difference is between persons who have headaches repeatedly and those who do not. In order to do this we have been for some years now taking samples of the pulse wave contours of subjects who never [illegible] had headaches and comparing them with the pulse wave contours of a representative cranial artery of individuals who have headaches, taking samples from the latter both during those periods when the headaches are not occurring and when headaches are present.

It has become quite evident that the individual who does have attacks of migraine, even when not having headaches, is somehow [illegible] his cranial vessels from minute to minute, hour to hour, day to day [illegible] adjustments that he is making to his environment, which is exhibited [illegible] variability of the pulse wave contours as well as of the lumen of the blood vessels.

In general, when a [illegible] cranial [illegible] structures [illegible] headache [illegible] size of [illegible] is that of a person [illegible] remarkably constant as regards the size and shape of pulse wave contours. [illegible] A person who never has headaches [illegible]

Interestingly too, we have attitudes and behavior patterns commonly occurring in such individuals who have attacks of migraine headache. These behavior patterns are characterized by compulsive, repetitive and excessive activity, bordering in some cases on the pathological but

The figure of 70 per cent penetrance was obtained from the fact that of the 65 offspring of parents both of whom had migraine, only 45 or 69.0 per cent, had headaches. On the assumption that migraine is due to a recessive gene, 100 per cent penetrance would result in 100 per cent affected offspring when both parents had migraine.

If migraine were dependent on a recessive gene with 100 per cent penetrance, we would expect 25 per cent of the offspring of two heterozygous parents to show the trait.

In order to rule out possible accidents, such as phenocopies, pedigrees with one affected person only were discarded. Data from families of propositi were corrected for bias using the method of Haldane (8). Migraine was found in 15.4 per cent of the sibs of the propositi and in 37 per cent of the sibs of affected individuals who were not propositi.

There are two main sources of error in these data reflected in the percentages of 15.4 per cent for the frequency of migraine in the sibs of propositi and of 37 per cent for the frequency in the sibs of non propositi. Propositus data are low because the age of onset is relatively late—in general over the age of 20 for about half of those who have migraine. On the other hand, a bias in the opposite direction is that the non propositus data are too high because all headaches in older relatives remembered by propositi may not have been migraine, although effort was made, as described above, to exclude these by insistence on careful descriptive data.

When analysis was carried further, combining the calculations for propositi and non propositi, weighting by the sample size and correcting for penetrance, the proportion of affected offspring from a mating of two heterozygotes turned out to be 29 per cent. On the basis of calculations of the variance of the estimate, this is not significantly different from the expected ratio of 25 per cent manifestation of a recessive gene.

Comment

There exists the alternate possibility that migraine headache is due to a dominant gene with partial penetrance rather than to a recessive one. The difficulty of such a hypothesis is that it is essentially untestable. Such an assumption can be made for every human trait without inspection of the data, since a dominant trait with partial penetrance can explain any sort of data. Such a possibility must then be left open, at the same time realizing that it is an unfruitful and untestable hypothesis.

SUMMARY

In summary, therefore, highly significant evidence has been offered to demonstrate the hereditary character of migraine and to permit one further

to a some correctly that the inheritance of the migraine headache trait is through a recessive gene with a penetrance of approximately 70 per cent

DISCUSSION

DR. LAURENCE H. SNYDER (Norman, Oklahoma): I would like to ask Miss Goodell if she considers migraine an allergic manifestation and, if so, whether any tests or searches for allergy in the other members of the family, especially when a parent of a migrainous person did not have migraine, were made.

PRESIDENT HOOKER: We have a question from the floor from Dr. D. J. Simons of New York: "Would Miss Goodell or Dr. Wolff indicate what features resulting in the migraine headache attack are inherited by the patient?"

DR. HAROLD G. ... not happen to be o... most attacks and w... the patients.

The second question raised by Dr. Simons indicates, quite rightly, an uneasiness on the part of a ... represe... in the ... the m... e ... a feature that gives rise to this disturbance.

We have looked at this at three levels: first, as regards the actual change in the body that is pertinent to the pain, and it has become evident, and I think that most will agree, that the factor that is relevant to the pain is the contractile state and dilatation of the cranial vasculature. There are a host of details missing as to the exact vessels and the precise nature of the disturbance ... who have headaches repeatedly and those who do not. In order to do this we have been, for some years now, taking samples of the pulse wave contours of subjects who never had headache and contrasting them with the pulse wave contours of a representative cranial artery of individuals who have headaches, taking samples from the latter both during those periods when the headaches are not occurring and when headache is present.

It has become quite evident that the individual who does have attacks of migraine, even when not having headache, is somehow involving his cranial vessels from minute to minute, hour to hour, day to day, in adjustments that he is making to his environment, which is exhibited in the variability of the pulse wave contours as well as of the lumen of the blood vessels involved.

In general, when a person is approaching a headache or is having a headache, the involved cranial vessel dilates and in this way it directly or indirectly stimulates the pain sensitive structures in its environment and within its walls. Even when the individual is not having a headache the size of the lumen of cranial vessels is much nearer that which is usually painful than is that of a person who does not have a headache. A person who never has headaches is remarkably constant as regards the size and shape of pulse wave contours.

Interestingly, too, certain attitudes and behavior patterns commonly occur in such individuals who have attacks of migraine headache. These behavior patterns are characterized by compulsive, repetitive and excessive activity, bordering in some cases on the pathological but

in many instances remaining well within acceptable and ostensibly healthy and successful adjustment most of the time. *Such individuals, however, often meet their threats as they* perceive them with a capacity to develop attitudes which prevent them from making a reasonable adjustment and from releasing their tensions in a predictable way. It is this aspect of the individual involving rigidity of attitudes and over-expenditure of energy which can be modified, *that I think explains why there is not a hundred per cent of persons with both parents who* have migraine headache, who themselves develop migraine attacks, and why many individuals either spontaneously or by contact with a physician can modify their attitudes and behavior and thereby alter the frequency and intensity of this painful state.

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CHAPTER XXI

THE GENETICS OF PSYCHOTIC BEHAVIOR PATTERNS

FRANZ J. KALLMANN[1]

INTRODUCTION

Along with the advent of modern psychiatry at the end of the last century, it became necessary to look for genetic components in the etiology of psychotic behavior patterns. The rationale of the resultant investigative work rested on the observable fact that not all human beings showed a tendency to mental disorder simply because they were intermittently exposed to the light of the moon. This observation indicated the need for research into possible gene-controlled deficiencies in the structure of apparently ill-adaptable types of personality, but the execution of the task proved to be neither simple nor popular.

By its very nature, the genetic approach ended those carefree days when mental illness, for want of a better label, was called lunacy and ascribed to the disturbing effect of an idle goddess. In short, genetic studies made it impossible to maintain the comfortable, if not comforting, notion that a potentially evil omnipresent force in human existence controlled the destiny and affairs of men through psychic contagion from above or some other mysterious means.

Ample proof has been accumulated during the intervening years to support the tenet that the potentialities of a major psychosis, while dependent on certain characteristics of the human species and tending to vary in expression according to ethnic, cultural or general ecological group differences of mankind, are not actually concomitant with any of these broad designations. It is undeniable that only human beings are able to respond with a true psychosis to distressing environmental circumstances. Yet there is abundant evidence to show that not all of them will do so.

Many persons are capable of adapting themselves to extreme stress conditions without developing a progressive psychosis, despite the fact that they may come from family units or cultural areas which produced a severe psychosis in a different member of their group. On the other hand, some

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of the vulnerable persons just seem to slide into a psychotic behavior pattern with no previous history of unusual stress

To be sure, many quantitative and qualitative differences can be seen not only in the psychotic symptoms established but also in the bodily defense reactions mobilized against them. By the same token, no one would deny that an unfavorable environment may precipitate a given type of psychosis in a certain number of non resistant persons, or conversely, that mental illness may have an adverse effect on the social status of the family.

Nevertheless, the incidence of mental disorder is observed in all segments of the human population, regardless of social, economic or cultural status. It occurs in slums as well as in royal families, and not even psychiatrists can be sure of having only well adaptable offspring. Indeed exceptionally fine parents are known to have had a schizophrenic child, and there are many schizophrenic mothers who have phenotypically normal children.

Generally speaking, psychotic behavior disorders seem to follow selective patterns of distribution and cannot be explained either by a universal species vulnerability or by general emotional group experiences. Since these disorders affect only some members of some families under nearly equal conditions of stress, it follows that the key to persisting obscurities in their etiology must be sought in certain specific disarrangements of those maturational, integrative or regulative functions which determine the adaptive capacities of a human organism.

Genetically, it has to be demonstrated that the tendency to develop a severe psychosis is specific in nature, that it follows a statistically predictable pattern of distribution, and that it increases in proportion to the degree of blood relationship to a family member affected by the given type of psychosis. According to the principles of organic inheritance, gene controlled phenomena cannot take place without the factor of blood relationship.

INVESTIGATIVE PROCEDURE

In procuring evidence *for a sliding scale of morbidity or expectancy* rates correlated with the degree of consanguinity, two reliable procedures are available. One is Weinberg's (19) system, which consists of the proband and sibship *methods. The other is the twin study method.* Weinberg's procedure seeks to determine whether or not a given trait occurs more frequently in blood relatives of a statistically representative number of persons *disclosing clinical evidence of that trait than it does in the* general population or, more precisely, in a group of persons not related to index cases by blood.

The twin study method provides an equally effective sampling procedure

In addition the use of this method makes it possible to study adjustive variations displayed by different genotypes in a controlled environment, or by a constant genotype under the influence of different environmental conditions

As may be expected however twin studies have certain limitations too Difficulties arise in particular when an attempt is made to separate an individual's immediate environmental circumstances from the hereditary components of his existence, or when there is a tendency to postulate a one-sided type of causality in the relationship between genetic and nongenetic influences There is no doubt that even in one-egg twin partners each has a complete ego of his own Once he has come through the ordeal of being born he is biologically undistinguished from single born individuals Obviously however one-egg twins cannot be separated before they are born nor can they be provided with two mothers of different age, personality or status of health

Likewise two-egg twins are no more dissimilar genotypically than brothers and sisters and like them are rarely raised in different cultures Therefore even fraternal twins are unlikely to fall into the extremes of possible genetic and cultural differences For this reason they are limited in their usefulness as control subjects when it comes to traits which are known to depend largely on the environment

In view of the complexity of problems encountered in the analysis of family data on psychotic behavior patterns it is indeed fortunate that the advantages of the Weinberg and twin study methods can be combined in a procedure which extends the number of genotypically dissimilar sibship groups to be compared under similar conditions of culture and home milieu The six groups compared by means of the twin family method are one-egg twins two egg twins of the same sex two-egg twins of opposite sex, full sibs half sibs and step sibs This method has been used in most of our own recent family studies At the present stage of knowledge and techn...

RECENT RESEARCH DATA

The statistical details of our analysis of the distribution of psychoses in schizophrenic (953) manic depressive (75) and involutional (96) twin index families were presented in several recent publications (Kallmann, 8 9 10 11) It seems desirable therefore to emphasize here the general genetic inferences to be drawn from these data as well as from a few additional reports which have appeared in the meantime particularly those of Flesser (2) Rado (13) Schulz (14) Slater (16 17) and Stenstedt (18)

Elsässer's study of a total of 134 single born sibships with two psychotic parents included the offspring of 54 matings of two clearly schizophrenic (34) or two clearly manic depressive (20) parents. While the psychosis rates of the offspring were generally somewhat lower than those reported by other investigators, they fell between 30 and 40 per cent, which is distinctly higher than the expectancy of persons with only one schizophrenic or manic-depressive parent.

Even more striking was the fact that the psychoses observed in the children seemed to follow strictly the pattern set by their parents. The crucial theory of specific genetic mechanisms for the two major types of psychosis was thereby confirmed. Agreeing with this finding, the results of our own study revealed neither a twin pair with a schizophrenic psychosis in one member and a manic depressive psychosis in the other, nor a single manic depressive index family with an authentic case of schizophrenia among the parents and siblings of the index cases. On the whole the recently published observations of Slater (16, 17) and Stenstedt (18) point in the same direction.

The observed trend, therefore, is toward an increased incidence of schizophrenia in the relatives of schizophrenic index cases and toward an increase of manic depressive psychosis in *the relatives of manic-depressive* index cases. Only the relatives of persons affected by an involutional type of psychosis tend to show an increase in both involutional and schizophrenic *psychoses. As indicated by expectancy rates varying from* 6.0 per cent for the sibs and two egg co twins to 60.9 per cent for the one egg twin partners of involutional index cases, the increase in involutional psychoses is rather pronounced.

The schizophrenia rates for the same group of families, although somewhat above those for the general population, are considerably lower than the rates observed for the relatives of schizophrenic cases. The incidence of manic depressive psychosis in these families is not increased at all. In other words, there is no evidence of a genetic relationship between the entity of manic depressive psychosis and the symptomatology of involutional melancholia or similar non periodic forms of depressive behavior in the involutional period.

Genetically, it may be inferred that the development of an *involutional psychosis* requires not only the capacity *for survival into later years without* psychosis, but also a certain form of emotional instability which reaches the threshold of a psychosis only under the age specific impact of cumulative emotional strain and insecurity, that is, in combination with progressive impairment of general adaptability. The clinical specifications of this type of instability are met especially by the characteristics of schizoid personality traits genetically identified as the least resistant phenotypes of

heterozygous carriers of the schizophrenic genotype The implication here would seem to be that the principal genetic derivation of involutional psychosis is from an indirect relationship to the entity of schizophrenia, and not from a specific type of predisposition producing a particular impairment of the adjustive plasticity of aging persons

By contrast the potentialities of a *cyclic psychosis*, when adequately defined are distinguished by the specific ability of a group of vulnerable persons to exceed the normal range of emotional responses with extreme but self limited mood alterations The morphological substrate of the given dysfunction seems to be associated with a subtle disturbance in a neurohormonal control mechanism which ordinarily protects man s emotional life from harmful extremes of affective responses The regulatory instability produced by this dysfunction has been shown to be correlated with the genetic factors for gout and diabetes with a relatively high degree of resistance to tuberculosis and with a general tendency to obesity and cardiovascular disorders It should be stressed however that present information as to the biochemical constituents of the underlying genotype as well as the range of its compensatory adaptiveness is still far from complete

Regarding the mode of inheritance which classifies the potential vulnerability of cyclically reacting persons the available evidence points to simple autosomal dominance with incomplete penetrance In all studies conducted so far significant differences have been observed between the general population rate which usually does not exceed 0 4 per cent and the morbidity rates for relatives of cyclic index cases According to Stenstedt s family data (Stenstedt 18) the expectancy of the parents sibs and children of manic-depressive probands approximates 15 0 per cent In our twin family study (Kallmann 11) the comparative sibship rates have shown variations from 16 7 per cent for the half sibs to 22 7 per cent for the sibs, 25.5 per cent for two-egg co twins and to nearly 100 per cent for one-egg twin partners The corresponding rate for the parents is 23 4 *per cent*

The relative infrequency of the disorder in modern populations seems largely due to factors of selection which reduce the reproductive rate of the carriers without affecting the social level of their families (Kallmann Stenstedt) At least there seems to be *no tendency toward a social decline* of the magnitude typical of schizophrenic family units

u sor itred behavior patterns by a metabol c disturbance in the enzymatic range The consequent vulnerability can be described psychodynamically as a person s inability to be a

part of the milieu in which he lives" (Hinsie 5, p. 249), or as an integrative pleasure deficiency which leads to adaptive incompetence (Rado 13).

Nevertheless it has been shown by Braceland (1), Hoskins (7) and others that the primary physiodynamic substrate of the disintegrating process is in a state of baffling obscurity. Additional uncertainties are related to a wide range of variations in age of onset, the duration and persisting severity of clinical symptoms, and their varying distribution between the sexes.

From a genetic standpoint, the specific homogeneity of the genotype is indicated by the observation of different types of symptom formation not only in one-egg twin partners and other members of the same family unit, but also in affected individuals at different times. The theory of a recessive mode of inheritance is particularly supported by the distribution of the disorder in affected families, which is likely to be subject to factors of selection in mating and reproduction, and by an excess of consanguineous marriages among the parents of schizophrenics. In this connection it should be noted, however, that Penrose (12) and Schulz (14), in particular, have not been fully convinced of the apparent uniformity and simple recessiveness of the main genotype.

The fact that the prevalence of schizophrenia in normal populations and proband families differs significantly is undisputed. In the absence of special conditions of inbreeding the general expectancy is no lower than 0.7 and no higher than 0.9 per cent. The corresponding rate for relatives of schizophrenics varies from 7.1 per cent for half sibs, through about 14 per cent for full sibs and two-egg co-twins, to 86.2 per cent for one-egg twin partners. Children of one schizophrenic parent have an expectancy of 16.4 per cent, while the incidence among the parents of schizophrenic index cases is 9.3 per cent. Next to one-egg co-twins, the children of two schizophrenic parents have been found by all investigators to have the highest expectancy of the disease.

The pronounced variability in the clinical expressions of the genotypical dysfunction apparently depends on the interaction of general constitutional modifiers and those precipitating outside factors which arise from uncontrolled imperfections in the structure of modern societies. Measurable correlates of this graded deficiency in resistance may be seen in the capacity for mobilizing effective mesodermal defense reactions, in the compensatory power of the athletic component of physique, and in the ability to maintain a stabilized level of body weight.

The main homozygous variations in the phenotype range from a degree of resistance sufficient for the complete control of the basic dysfunction, through intermediary states of schizoid personality changes and relatively mild psychotic processes, to extreme lack of resistance characterized by

total disintegration or death Living under ordinary conditions, heterozygous carriers can only have either a schizoid or a normal type of personality However, if exposed to extreme stress or to the effect of such toxic compounds as mescaline and lysergic acid (Hoch, 6), heterozygotes and highly resistant homozygotes may break down with a schizophrenia like reaction syndrome or a real schizophrenic process, respectively

As for possible genetic elements at the roots of *psychoneurotic traits* and various *psychosomatic vulnerabilities*, it can only be mentioned here in passing that current information in this important area of psychiatric genetics is the least complete In Eysenck s opinion (3), many differently formulated theories of neurosis are on the same descriptive level and are concerned with the same fundamental dimension of personality In collaboration with Prell (4) he was one of the few investigators of psychoneurotic reaction patterns (outside the field of criminality) to avail himself of the opportunities afforded by the twin study method On the basis of their study of 25 one-egg and 25 two egg pairs Eysenck and Prell classified the neurotic personality factor as a biological and largely gene specific entity estimating the genetic contribution to this neurotic unit predisposition at 80 per cent

According to Slater s twin observations (16 17) psychoneurotic symptoms are less closely related to a given type of stress than to the basic personality His working hypothesis is that such personality variations as determine psychoneurotic reaction patterns are graded in their type of distribution and are somehow traceable to the effect of polygenic inheritance Broad as it is this theory seems plausible enough to indicate the need of much additional work by means of well-organized twin family studies

Theories of simple dominance or recessiveness are also inconclusive when it comes to mental disorders which are peculiar to the senium, with the possible exception of some specific types of *pre senile brain atrophy* (Sjögren et al 15) Apparently the etiology of the usual *forms of a senile psychosis* is based on an interplay of complex determining factors among which are age susceptible personality traits reduced adaptive plasticity, and those gene specific biochemical phenomena which *control growth* and decline (Kallmann 10)

SUMMARY

In conclusion it may
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phenomena experienced

ue genetic approach aims

at supplying adequate answers to questions of why a particular member of a particular family at a particular time will undergo these particular experiences, and why other members of the same unit will not

In so doing, genetic studies have in many instances succeeded in confirming the belief, at least theoretically, that mental disorders are both preventable and potentially curable At the same time, such studies have again focused attention on the importance of a systematic and well balanced approach in any attempt to reach the given goals It is now clearer than ever that only when attitudes of optimistic complacency toward the causes of severe maladjustment give way to a realistic awareness of the incompleteness of knowledge regarding the genetic aspects of psychotic behavior patterns, will further significant progress be made

DISCUSSION

DR NOLAN D C LEWIS [New York N Y] I should like to emphasize what you are already aware of that this brief report is a very concentrated account of many years of research that Dr Kallmann has made on the subject

I think we all realize too in view of the attitude of contemporary psychiatry that an almost overwhelming amount of factual evidence must be accumulated to establish any acceptable genetic theory of mental disorder Psychogenic theories are now favored and hold that the heredity factors presented by others may be more apparent than basic or are otherwise explainable Since disturbances in the family life and other human environmental factors affect the child adversely the idea of social inheritance rather than gene inheritance is preferred However it should seem obvious to those who have read or heard such evidence as has been presented today that psychogenic factors alone do not explain Dr Kallmann's data on monozygotic twins as compared with those on dizygotic pairs and sibs It would seem that most of the prejudice against genetic inheritance stems from a feeling in the realm of wish fulfillment based on the idea that acceptance of genetic factors would create an attitude of therapeutic hopelessness

Those who have followed Dr Kallmann's publications during the past years know that he recognizes and includes other factors in the organization of the total behavior pattern and insists that therapeutic procedures are most important

Another matter should be mentioned Families of patients suffering from disorders that are primarily genetic such as have been discussed today should be informed as accurately as possible A significant number of these families would voluntarily limit the family size or increase it as the case might be if they had some facts at their disposal They might thereby reduce the contribution to these diseases and also would be in a better position to care for the children they already have

Another aspect of the problem concerns sufferers from these disorders themselves who may live with misconceptions and misinformation resulting in a serious psychological handicap, the removal of which would afford considerable relief Many such persons are not aware of the possibilities of prevention or modification nor do they understand that there are various degrees of expression in nearly all of the inherited disorders that are known about at the present time

CHAIRMAN WHITEHORN I have received a question from Dr Kety How does Dr Kallmann answer the criticism that monozygotic twins as the result of physical identity parental attitudes etc create a unique socio-environmental setting which favors concordant mental disturbances? '

I would also like to ask Dr Kallmann a question, bearing on the predisposition to develop schizophrenic illness. For many years clinicians have been interested in a so-called schizoid personality In the American textbooks and in the oral tradition in American psychiatry, this term has come to mean something apparently quite different logically from what Bleuler had in mind It has come to imply rather more a seclusive autistic disposition, asocial in some ways whereas with Bleuler, if I have understood him correctly, it meant something contrasted with the syntonic disposition, a disposition on the part of the schizoid person to experience life in a more loosely organized ambiguous not so clearly perceived fashion, whereas the syntonic person beats out of life, perhaps a little artificially, a rather highly integrated experience at each phase of his existence

I am very curious to know if, in the genetic studies bearing on predisposition, either of these concepts of the schizoid personality seems justified by the facts as having a close relation to the occurrence of schizophrenic illness

I have one more question here "What is the actual incidence of inheritance in manic depressive disorders, and similarly, genetic factors in schizo-affective disorders?" This is from Dr S H Epstein of Boston

Dr. Franz J Kallmann (Closing) The thought provoking comments of Dr Lewis do not seem to be in need of further elaboration They penetrated to the core of the ancient *nature-nurture controversy* and I am sure, were appreciated by all of you because of their forthrightness

Dr Kety's question was dealt with as a crucial issue in the original report and thus can be answered by underscoring some of the previous statements It is correct that one-egg twins form a unique socio-environmental unit which may favor the manifestation of concordant mental disturbances by providing similar precipitating elements of causation However, parental attitudes and other distinguishing features of the *environmental settings* of two-egg pairs or ordinary sets of sibs have not been found to differ so distinctly as to explain a discordance rate of approximately 85 per cent for adult forms of schizophrenia in the absence of monozygosity (similar heredity) The same is true for nearly 60 *per cent of one-egg twins* with respect to very early (pre adolescent) forms of schizophrenia In the vast majority of these discordant sets two twins (or sibs) live with the same mother and the same father *and are* raised with similar methods of toilet training and other upbringing procedures. Although we have paid a great deal of attention to potential factors of modification in the life histories [illegible]

[illegible] of [illegible] ... of the most pertinent and most [illegible]

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at supplying adequate answers to questions of why a particular member of a particular family at a particular time will undergo these particular experiences, and why other members of the same unit will not

In so doing, genetic studies have in many instances succeeded in confirming the belief, at least theoretically, that mental disorders are both preventable and potentially curable At the same time, such studies have again focused attention on the importance of a systematic and well balanced approach in any attempt to reach the given goals It is now clearer than ever that only when attitudes of optimistic complacency toward the causes of severe maladjustment give way to a realistic awareness of the incompleteness of knowledge regarding the genetic aspects of psychotic behavior patterns, will further significant progress be made

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CHAPTER XXII
GENETIC ASPECTS OF ADAPTABILITY

H. BENTLEY GLASS[1]

It is rather commonly said that man excels all other species in adaptability, and that this, and almost this alone, marks his evolutionary superiority and entitles him to a place in the vanguard of evolutionary progress. It is startling, then, considering that adaptability is acknowledged to be so important an evolutionary—and so peculiarly a human—trait, to find that very little investigation has been made of its genetic basis. This is partly through a failure to clarify the relevant concepts, and partly through a failure to develop and apply effective methods of genetically analyzing the problem. The former should obviously precede the latter in the general investigation of adaptability.

Paul Weiss (14) has noted the dual meaning of the term *adaptation*, which sometimes is applied to the state that results from appropriate adjustments to conditions, and sometimes to the process whereby the adjustments are brought about. To resolve this ambiguity, he has proposed to call the state that is achieved *adaptedness*, and to reserve the term *adaptation* for the process. This usage will be followed here.

If adaptation means the effective process whereby living organisms make or undergo appropriate adjustments to conditions, this may either be temporary, by means of modifications of their original state made by individuals or groups, or may be more lasting, by means of genetic changes of the species or population through the action of natural selection on mutations. Adaptability may be defined as the capacity to make such changes, whether temporary or lasting, whether individual modification or hereditary change. Adaptability has also come to have a dual, somewhat confused meaning. On the one hand, the capacity to adapt may be possessed uniformly by [illegible]
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the eye by me [illegible]
become genetically fixed, being the common product [illegible] adaptability has occur within the species. On the other hand, there may be genetic variability in this respect within the species (i.e., differences between various [illegible] pt) or even within a population

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exists at this point on the clinical classification of schizoid personality types, mainly because of the lack of adequate diagnostic criteria

With respect to Dr Epstein's request to repeat the series of percentages offered as to "the actual inheritance incidence in manic-depressive disorders", may I re-emphasize that the observed concordance rate of nearly 100 *per cent for one egg twin pairs is probably an artificial* maximum value, due to the fact that our series of manic depressive twin index cases consists only of hospitalized patients For the half sibs, full siblings and dizygotic co twins of manic *depressive subjects, the comparable expectancy rates are 16 7, 22 7 and 25 5 per cent, respec* tively Nearly 60 per cent of cyclic index cases come from matings of one normal and one manic depressive or cycloid parent According to Stenstedt, the total "morbidity risk for manic-depressive psychosis" among the parents siblings and children of manic depressive index cases (calculated collectively) is about 15 00 per cent

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18 S[illegible]

19 WEINBERG, W [illegible] 812, 1930

types of differences in capacities to respond. Studies of genetic differences in simple physiological responses ought to precede the study of genetic differences in simple reflexes and studies of the latter should precede those of more complex aspects of learned behavior.

It might be expected that hereditary differences in relatively simple capacities to respond would have been studied in the human species to a considerable extent, but this is clearly not the case. Apart from the investigation of tasteblindness to phenylthiocarbamide little has been done and even that condition is not attributable with certainty to a single gene difference. The difference between caucasoids and negroids in the hereditary difference in skin color has also not been completely analyzed genetically, although it seems certain that the number of gene differences concerned is few (one to three) and that these genes act additively. Yet it has not been determined whether these racially differentiated genes certainly possess adaptive value, and if so, whether they substitute adaptedness for adaptability by mutual replacement or, on the other hand, by superimposing the genes causing *adaptedness upon a now masked but still present constellation* of genes responsible for the adaptability. In other words, do negroes still possess the underlying capacity to darken in skin color upon exposure to ultraviolet radiation? The most recent and extensive reviews of the subject of skin tanning leave the answer unclear (3, 4).

For many types of simple response it is not even known whether there is a genetically determined portion of the observable variability, or whether it is entirely attributable to environmental conditions. A broad survey of characteristic types of response ought to be undertaken with this end in view. Analyses of pedigree data would require tremendous labor without a certain return, whereas the type of investigation of individuals undertaken by R. J. Williams (15) and his group at the University of Texas in the last several years reveals tremendous and characteristic individual variability without providing assurance of its genetic nature. A modification of the co-twin control method first advocated by Gesell and Thompson (8) and by Blakeslee and Banker (2) is simpler and far more promising.

A brief discussion of this method may be found in the excellent analysis by Price (10) of primary biases in twin studies. The method seems to have been first practiced by Walcher (13) and Elsasser (6), who tested the effect upon a pair of newborn, presumably monozygotic twins of lying in *different positions, either on the back or on the side* for most of the time. They succeeded in demonstrating that the former position made the index of head shape significantly ...
made the index of head sh...
more readily possible to r... ...shape in a brachycephalic direction. Thus one twin's index decreased in 16 days from 88.39 to 85.12 (more

(i e , differences between individuals in capacity to adapt) For example, in the species *Homo sapiens*, certain ethnic groups appear to possess genes that make them almost uniformly dark skinned regardless of where they live, whereas other ethnic groups possess genes that endow them with the *capacity to form melanic pigment in the skin, but in large amounts only* if and to the extent that the skin is exposed to ultraviolet radiation To make the necessary distinction between these two types of conditions, I propose to call the capacity to adapt that is uniformly possessed by all members of the species *homogeneous adaptability* and to call the diversified type *heterogeneous adaptability*

These relations clearly imply something about the respective environments *the fixed and invariant trait can be adaptive only in an environment* that in respect to the relevant conditions is also relatively fixed and invariant, the variable adaptive trait is adaptive in relation to a variable environment The interplay between the evolutionary and ontogenetic aspects of this relationship has been admirably depicted by Paul Weiss

> If organisms were rigidly preadapted to fit precisely one particular detailed course of life their chances of ever encountering just that one expected course hence of surviving would be infinitesimally small *Here* then is the limit beyond which evolutionary prefitting may not go without dooming its creatures The precision of fit must not exceed the precision with which future conditions can be predicted and since predictability is but another expression for the regularity of past recurrences we realize that what an organism is prefitted for by its evolutionary endowment is merely a statistical norm of conditions the standard range of which is relatively constant the individual manifestations of which however vary at random from case to case The gross lines are predetermined but the details are left indeterminate for the individual organism to fill in according to the contingencies it will meet
>
> (From *Adaptation* pp 8 9 John Romano, ed)

The capacity of organisms of particular species to respond in *a certain* appropriate manner to a change of conditions grades from the simplest sorts of physiological responses, through tropisms and simple reflexes, into complex instincts and patterns of conditioned reflexes until it reaches a maximum in the conscious behavior of the most intelligent vertebrates The possibility of making a genetic analysis of differences in such capacities is limited, however, as in all genetic analyses, to those differences which exist between *forms* that may be hybridized At least for the present, we must continue to operate on the assumption that differences of larger magnitude in capacities to react depend upon hereditary factors of the same nature as those which can be demonstrated to produce differences within single species or between species that may be intercrossed It also seems most likely that *progress in understanding the genetic basis of adaptive* capacities will be derived from studies that investigate first the simpler

to 40 per cent below the recommended allowances of thiamin. One twin of each pair was given 2 mg of thiamin daily over and above the amount contained in the regular home diet, the other twin receiving a placebo, and the twins were measured in height and weight and were given various mental tests. At the termination of 4½ months, the thiamin fed twins seemed to show a significant superiority in weight and height, and perhaps in manual dexterity and retention tests. But after 9 months no significant differences were apparent. In spite of the negative results, this was an elegant demonstration of the method, and permits the conclusion that in average north American homes the daily supplementation of children's diets with thiamin is not likely to influence physical or mental growth within a 9 months' period.

Unfortunately, the co twin control method has up to now been limited, in human genetics, to the study of differences in the effects of early and deferred training or of parallel training by different methods, of a very few pairs of twins. Cattle geneticists (e g, Bonnier and Hansson, 5, New Zealand Dairy Board, 9) in Sweden, New Zealand, Scotland, the United States and elsewhere have begun to use to greater effect the unparallelled experimental material provided by nature in the form of monozygotic twins although even in these relatively long term experiments, the procedure has usually been simply to expose one twin to the experimental condition to be te[illegible]

For example in B[illegible]

diet and the other [illegible] plemental diet. The two co twins were kept in adjacent stalls during the course of the experiment, and the principal character studied was gain in body weight.

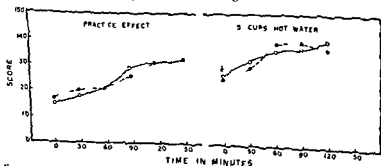


Fig. 70 Scores of the monozygotic twins Albert and Andrew on at[illegible] vision test. L[illegible]
impr[illegible]
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}[illegible]

dolichocephalic) while the others increased from 85.08 to 88.35 (more brachycephalic). Although the changes were quite uniformly producible in additional cases (three pairs of dizygotic twins and a series of other newborn infants), the permanence of such early treatments remains questionable.

A modern and perfectly planned example of the co-twin control method was reported by Robertson, Latham, Walker and Weaver (11) who studied 36 pairs of monozygotic twins (aged $7\frac{1}{3}$ to $15\frac{1}{2}$ years) over a period of $4\frac{1}{2}$ months and 25 of these pairs for a full 9 months. Of the 36 pairs, 5 were living in well-to-do homes, 28 were of fair to moderate circumstances, and 3 were poor. Half of those checked were eating diets 20

PRECISION TESTS

SERIAL NUMBER

NATURE OF EXPERIMENT

DATE

TOTAL

NAME

AVERAGE

needle as the implement ... subject ...

... ot. The targets measure 1 cm ... the lines surrounding ... points. Total for each test 200

points. Time required less than ...

to 40 per cent below the recommended allowances of thiamin One twin of each pair was given 2 mg of thiamin daily over and above the amount contained in the regular home diet the other twin receiving a placebo, and the twins were measured in height and weight and were given various mental tests At the termination of $4\frac{1}{2}$ months, the thiamin fed twins seemed to show a significant superiority in weight and height, and perhaps in manual dexterity and retention tests But after 9 months no significant differences were apparent In spite of the negative results, this was an elegant demonstration of the method, and permits the conclusion that in average north American homes the daily supplementation of children's diets with thiamin is not likely to influence physical or mental growth within a 9 months' period

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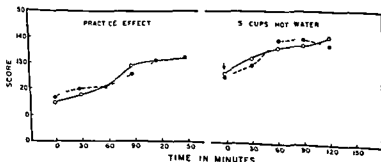


Fig 70 Scores of the monozygotic twins Albert and Andrew on the muscular visual precision test Left under standard conditions after preliminary training to show the steady improvement over a $2\frac{1}{2}$ hour period The next day subjects would [illegible] scoring about the same as at [illegible] one twin had drunk 5 cups [illegible] essentially the same as in th[illegible] hot water was taken [illegible] the time at which the

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DATE — TOTAL

NAME — AVERAGE

Fig 69 Score sheet for the muscular visual precision test. Ten shots are made on each target in rapid succession up to a total of ten targets with an ordinary laboratory dissecting needle as the implement. The subject rests his elbow on the table at a suitable distance from the [illegible]

points. Time required less than [illegible]

A simple preliminary study of this kind has been undertaken during the past year in the Mergenthaler Laboratories of Biology at the Johns Hopkins University, and will serve to illustrate the points just made. A pair of Senior undergraduate students, monozygotic twins, Polish by birth and educated in Switzerland, were much interested in human heredity and offered themselves as subjects for the experiment. Previous diagnoses showed them to be unquestionably monozygotic, although one twin is 2 inches taller than the other. One twin commonly takes the lead and is somewhat more aggressive in disposition, but intelligence tests administered by a psychologist who collaborated gave them both a rating of 119. The boys were asked to repeat the test (Wechsler Bellevue) using an alternative form, and each one was separately told just before starting that his co-twin had done 20 points better on the first test. One twin was obviously disturbed by the news, the other expressed his belief that an error must have been made. The first made an 8 point lower score on the second test than his co-twin. The one who was disturbed and affected as to score was the generally more disturbed and less emotionally stable one of the pair. This type of experiment gives interesting but not indefinitely repeatable results and demonstrates what might be done in analyzing the genetic component of the more complex forms of behavior.

A simpler situation was chosen for more repeated study. First a muscular visual precision test (fig. 69) was developed that could be run off in less than three minutes, and after some practice for purposes of standardization, it was decided to study the effects upon the response of caffeine, to which neither twin was accustomed. The general practice effect is shown in figure 70 A. It is evident that improvement with practice over a period

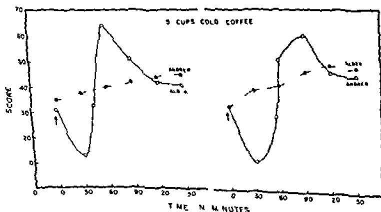
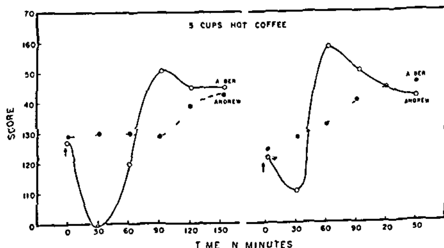


Fig. ... As in Fig. ... with the ... It is evident that the temperature ...

In short term experiments, on the other hand a much more efficient experimental design may be employed The two co twins may first be studied under standard conditions, and the level of inter twin variability determined Then twin A may be subjected to the experimental variable while twin B serves as control following which the experiment may be repeated with twin B as the experimental animal and twin A as the control The results, averaged over a sufficient number of trials, indicate (a) the degree of similarity in response to a given stimulus made by individuals of the same genotype and (b) the degree of variability under standardized conditions characteristic of individuals of the same genotype and a given degree of similarity of past experience A control group of individuals selected at random from the same population and corresponding to the twins in age and sex will further indicate the degree of variability in the response to the same stimulus to be found, within the same sex and age group in the entire population Studies of additional pairs of monozygotic twins would be desirable to define the upper and lower limits of variability found to exist between two individuals of identical genotype within a given population In this regard it should be emphasized that whereas Gesell (7) was fully justified in pointing out that the study of a single pair of twins is highly illuminating he was not correct in his belief that the method falls outside the calculus of biometrics The genetic variability in the capacity of response within a population can be most fully revealed by a study of the variance between pairs of twins in comparison with the variance within pairs of twins i e between co twins



e tle tu e at

wlicl tle coffee was t k

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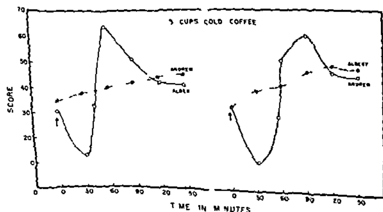


Fig. ? As in Fig. ? with the …

of 150 minutes was highly similar in the two twins Figure 70 B shows that consumption of a large amount of warm water by one twin but not by the other, had no effect on the scores made over the subsequent period Figure 71 A reveals the effect of the consumption of a considerable amount of coffee by one twin but not by the other While the control twin showed a characteristic steady improvement in score the experimental subject showed first a sharp decrease in precision about half an hour after taking the coffee then a very striking increase to maximal precision about 1½ hours after taking the coffee and finally a decline until the level of the control twin was reached Figure 71 B shows that exactly the same type of response occurred when the twins reversed their roles Figure 72 A and B shows that the same characteristic effects were produced after drinking *cold coffee instead of hot Temperature of the fluid had no influence on the response* Figure 73 A and B shows that the same characteristic responses were made by both twins when the tests were conducted with capsules containing respectively 5 grams of caffeine citrate or 5 grams of lactose The capsules were identical in appearance and the twins took them and were tested in separate rooms Finally figures 74 A and 74 B reveal the result of administering lactose or caffeine capsules respectively to a control group In general the subjects in the group getting the lactose capsules show a practice effect but the marked variability in their responses almost

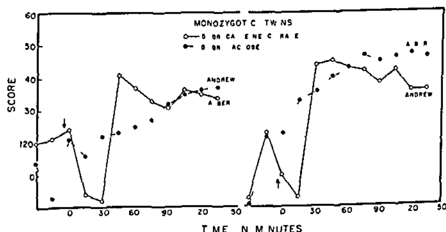


Fig 73 Scores of the [illegible]

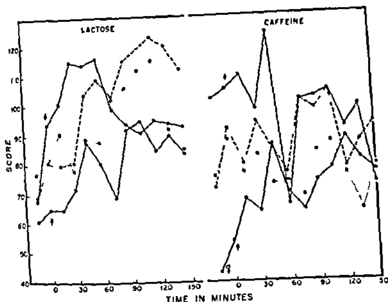


Fig 74 The responses to 5 grains of lactose or caffeine citrat ...
students and instructors tes ...
cation test and without reg ...
female was included among ...
rows indicate the respective times at which the capsules were taken

obscures it The variability in the group taking the caffeine is so great that no systematic trend can be observed

There is an extensive literature upon the pharmacological effects of caffeine It is not apparent how the clearly defined responses of the monozygotic twins are to be related to well known facts such as the following that caffeine increases the basal metabolic rate, the cardiac output, and the coronary flow and that in large doses it will induce fever by increasing muscular tone and reducing heat loss, that it increases gastric secretion, that it is a pronounced diuretic that it decreases cerebral blood flow, and that it increases positive conditioned reflex responses and decreases their extinction by lowering internal nervous inhibition The study of the successive changes in these respects in the same pair of twins would perhaps reveal some interesting correlations

Meanwhile the conclusion appears to be valid that the identity of response to caffeine on the part of the twins rests upon their identity of genotype and common experience To generalize safely, one would need more studies of pairs of monozygotic twins both reared together and reared apart yet even a single experiment with a result such as this implies

a very strong influence of heredity upon the nature of the response To extend this type of experimental design to the study of such responses as reaction time to visual, auditory, or tactile stimuli, and the influence of extraneous factors such as fatigue, seems an obviously promising method of beginning the study of the hereditary basis of adaptability

DISCUSSION

DR FRANK A BEACH [New Haven Conn] The only exceptions I would make to Dr Glass very stimulating paper are two in number Although in general it is probably true that problems of heredity and behavior are at present most fruitfully attacked by dealing with the simplest sorts of relations we can find it is nevertheless a fact that quite effective research has been conducted with fairly complex forms of behavior such as maze learning in the rat and trailing behavior in hunting dogs

Secondly, it strikes me as misleading to imply that any type of behavior, or any morphological character for that matter is *entirely* controlled by genic factors As has been pointed out earlier in these meetings the most powerful gene combinations do not act in vacuo and must have nongenic material on which to operate Furthermore the action of genes on nongenic substance occurs in a surround or environment which is never totally inert or lacking in effect upon the final outcome of interaction between genes and nongenic materials

If I may be permitted a sentence or two of propagandizing I would like to call the attention of this audience to a body of evidence recently summarized by Dr Calvin Hall in one chapter of the HANDBOOK OF EXPERIMENTAL PSYCHOLOGY edited by Dr S S Stevens and published in 1951 Describing a new discipline which he proposes to call psychogenetics' Hall brings together a large number of studies on the behavior of lower animals as a function of the genotype The arm chair debates about heredity and environment which used to be

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DR ARNOLD L GESELL [New Haven Conn] The method of co twin control in a sense falls without the realm of classical absolute mensuration It is a comparative clinical method an experimental device for analyzing biogenetic problems Nevertheless it has a unique kind of biometric validity and even statistical validity when one considers the vast number of variables which are equated in a single pair of highly identical twins The rich potentials of the co twin control method are convincingly shown in the paper by Dr Glass

DR H BENTLEY GLASS (Closing) In regard to the slight matters of disagreement raised by Dr Beach I won t endeavor to reply to the first one at all because I suspect that it is quite possible that I might be proved wrong Still I think that simple problems have received relatively so little investigation with this type of experimental material that they at least deserve inclusion

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in many of the papers before this one [illegible]

or environmental nature of a trait is entirely without meaning, and is the kind of question that one should not ask.

In response to Dr Gesell I fully agree that each pair of identical twins you study in an experimental situation like this is a unique experiment. If I should take another pair of monozygotic twins and test them by means of this same experiment for the response to caffeine it is quite unlikely that they will show the same characteristic depression followed by increased precision in the test, but I expect that they would show very great similarity. Over a sufficiently large number of pairs of monozygotic twins we can then get a measure of the variance between pairs of twins and the variance within pairs of twins which will make a meaningful statistical comparison.

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I am puzzled by what was stated to be the second disagreement because I thought that in my own wording I had been very careful to disavow any tendency *whatsoever to describe* behavioral traits or any other type of traits as entirely hereditary or entirely environmental and I spoke of monozygotic twins as having a common genotype *and* a common experience Of course, it is impossible to separate these I am in complete agreement with what has been said in many of the papers before this one, namely that the ordinary question about the hereditary

an existence which the child strives anxiously to maintain. It might be better to speak of it as *aloneness* rather than as withdrawal. The patient is an unrelenting guardian of his privacy. When he is left to himself, he can be happy, smile, hum a tune, play with his toys. When there is interference, he disregards it as long as he can. When the intrusion becomes too insistent, he fights it off with tantrums which appear to be the result of panic rather than anger.

The autistic child, ever ready to fend off other persons' encroachments on his capsulated inner world, is equally fearful of happenings in his surroundings which might necessitate a readaptation—that is, a modification on his part. Changes of routine, of the furniture arrangement in his room, of the accustomed route when he is taken for a walk can precipitate a major burst of deep distress. The sight of a broken toy, a crack in the wall, or some other deviation from completeness as conceived by the child can become a disturbing experience, long remembered and brooded over. The patient is extremely cautious in enlarging the scope of his activities, which are limited in number and repeated again and again. Resisting innovations, he struggles to live in a static world, and much of his behavior is governed by a powerful *desire for the preservation of sameness*.

Aloneness and obsessive insistence on sameness are the two principal diagnostic criteria of early infantile autism. All other symptoms can be explained on that basis. There is no felt need for communication. Some of the children have remained mute, though the rare utterances of a whole sentence in emergency situations certainly prove the ability to store up and use language. It takes the speaking children a long time before they enter upon anything resembling ordinary conversation. Parroted phrases are retained and later, in a sort of delayed echolalia, employed exactly as heard, even with the same intonation; this accounts for the phenomenon of pronominal reversals which persists for several years. Thus, when the child wishes to retire, he may echo a sentence used often by his mother: "Now I am going to put *you* to bed." Spontaneous language consists for a long time of rote enumerations and seemingly irrelevant utterances not intended for communication.

The child's relation to objects is better than that to persons. He can manipulate them in his own obsessive way. He is skillful and nimble in his handling of them. He has a phenomenal memory for arrangements and can after days reconstruct a complex block design. He can become angry at objects if they do not conform to his preconceived pattern. One of the children scolded the star shaped piece of the Seguin formboard because it was not up in the sky where stars belong.

Many are the peculiarities of autistic children. There are differences in degree and in the number and nature of accessory symptoms. But the de

CHAPTER XXIII

TO WHAT EXTENT IS EARLY INFANTILE AUTISM DETERMINED BY CONSTITUTIONAL INADEQUACIES?

LEO KANNER[1]

Early infantile autism was singled out in 1938 as a psychotic illness presenting a set of characteristics worthy of special consideration. The first observations were reported in 1943 (1). Since then, a sufficient number of patients has been studied in this country and abroad to substantiate the uniqueness of the syndrome. Our own case material (2, 3, 4, 5) now comprises exactly 100 children who can be so diagnosed with reasonable certainty. The common denominator consists of certain essential features *in a combination not encountered in any other disease.*

The first signs are noticed some time during the first two years of life. It would be difficult to pinpoint an exact time of onset. It is probably safe to *say that the emergence from the neonatal stage of biological helplessness* is not, as in the average infant, accompanied by a progressively differentiated contact with the human environment. Many mothers recall that they have never been able to 'reach' their child, who lay 'apathetically' in his crib and did not display an infant's usual anticipatory reaction when someone came to pick him up. Persistent absence of response to verbal address has almost invariably created the suspicion of deafness, which was later dispelled by otological examination and other evidences of normal hearing acuity. As the child grew older, the lack of response to attempted psychometry gave the impression of a markedly inadequate intellectual endowment; it must, indeed, be assumed that, prior to the delineation of *the syndrome, autistic children were regarded as severe mental defectives.*

This early self isolation has been compared to schizophrenic withdrawal. The analogy is not incorrect in so far as the clinical appearance is one of a child out of contact with the people about him. It is true that the histories of three or, at most, four of our patients indicate some preliminary reaching out of affective tentacles which were pulled in more or less abruptly within a few months before the end of the second year. But in most instances there never has been any real relationship with the mother or anybody else. The isolation is not so much an event or a process as it is a status,

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A statistical evaluation of the role of heredity is not easy if one thinks exclusively in terms of psychotic illness. To assure maximal *accuracy*, we have, for the purpose of this investigation, limited ourselves to parents, grandparents, uncles and aunts, and siblings.

Of the 200 parents, only one had a major mental illness, a postpartum psychosis following the birth of her autistic child's older sibling. One mother and one father were alcoholics, and one, who has a responsible secretarial position, is epileptic. One father, a prominent lawyer, had twice interrupted his college studies because of anxiety neurosis. Another father, a well known scientist, had convulsions in infancy and has marked digital tremors.

Of the 400 grandparents, a paternal grandfather, a paternal grandmother, and a maternal grandfather committed suicide. One maternal grandmother had an unidentified 'nervous breakdown' at 50 years, and one had Friedreich's ataxia. One maternal grandfather, a noted psychologist, was an obsessive-compulsive person, another had a 'nervous breakdown' at 30 years.

The number of the parents' siblings and entries about their histories of major illnesses are contained in 70 of our case records. Of the 373 uncles and aunts thus accounted for, a maternal aunt and a paternal uncle were schizophrenic, one paternal and one maternal aunt were depressed, two maternal aunts were feebleminded, two others (sisters) had a fear of leaving home, a paternal uncle had a psychotic episode while in college, and a maternal uncle and a paternal uncle were hospitalized for mental illness the nature of which could not be specified by the informants. One maternal

were a

mental

defectives.

Of the children's own 131 siblings, 117 were considered normal. Of the others, one each had epilepsy, sensory aphasia, mental retardation, specific reading disability, celiac disease, and Christian Schüller's disease. One is said to have perished from 'thymus death.' One can be des

has, in addition, a brother who shows marked schizoid tendencies in his behavior.

These figures indicate that, from a genetic point of view, it would be difficult to see a meaningful positive *correlation* between early infantile autism and the occurrence of psychiatric and neurological diseases in the patients' ancestries. However, our attention has been drawn to certain items which seem to us to be of great significance.

The autistic children come from intelligent, sophisticated stock. Of the

velopmental history and the two *pathognomonic features of aloneness* and insistence on sameness are always present and indispensable for the inclusion of any child in the category of early infantile autism.

There has been justified puzzlement about the nosological position of the autistic illness. Van Krevelen (6, 7) saw in it an oligophrenia with concomitant emotional defects. This assumption can be disproved by the observation that a few of the patients who functioned at an idiot or imbecile level in preschool age, achieved intelligence quotients of well over 100 in their early teens. The possibility of prenatal organic damage has been considered but thorough physical and laboratory examinations have yielded no consistent clue of any kind. The relation to schizophrenia is more difficult to determine. It is possible to regard early infantile autism as the earliest form of this illness, the specific features of which are influenced by the age at which they develop. Mahler (8) has distinguished convincingly between an autistic and symbiotic form of infantile psychosis, depending on the type of mother-child relationship. For the time being it seems practical to follow the advice given by Stern and Schachter (9) to study autism *as a specific phenomenon.* At any rate, the inclusion of these children in any broader diagnostic group would seem at present to shove such a study out of focus and to ignore the developmental and symptomatic peculiarities.

Of the 100 children of our series, 80 were boys and 20 were girls. The number of published cases other than our own is too small to allow any comparisons. But the ratio of 4:1 in the largest existing collection certainly indicates a male predominance.

The vast majority is made up of children of either Anglo-Saxon or Jewish descent. Not less than 27 were of Jewish origin. There was only a small sprinkling of patients who came of Italian, French, German, Scotch, or Irish stock. Clarification of this issue may come in the not too distant future from the fact that observations, as yet too sporadic, are beginning to be reported from European countries.

No generalizations can be made on the basis of the patients' physical condition or the circumstances surrounding birth. Difficult labor was reported in 11 cases: precipitous in 2, prolonged in 7, and placenta praevia in 2. Four were delivered by Caesarean section, and one sustained a fracture of an arm at birth. Difficulties in breathing were stated to be present in 3 of those and in 3 others who were delivered without mishap. As for congenital anomalies, one had a clubfoot, one had strabismus. One boy began having grand mal seizures at 5 years of age. Twelve were reported to have been premature; of these, 8 weighed less than 6 pounds at birth.

The position in the order of birth was distributed as follows. At the time when last seen, 15 were only children, 43 were first born, 23 were second, 13 were third, and 6 were fourth or fifth.

tively, but rarely step down from the pedestal of adulthood to indulge in childish play.

The void created by the absence of wholehearted interest in people is occupied by a devotion to duty. Most of the fathers are, in a sense, bigamists. They are wedded to their jobs at least as much as they are married to their wives. The job, in fact, has priority. Many of the fathers remind one of the popular conception of the absent-minded professor who is so engrossed in lofty abstractions that little room is left for the trifling details of everyday living. Obsessive adherence to set rules serves most of the parents as a substitute for the enjoyment of life.

This obsessiveness is a major contribution to the impersonal, mechanized relation with the children. The parents, apparently incapable of deriving pleasure from the children as they are, work for the attainment of goodness, obedience, quiet, good eating, earliest possible control of elimination, large vocabularies, memory feats. The child is essentially the object of an interesting experiment and can be put aside when he is not needed for this purpose.

It can be said only of a few of the autistic children that they were rejected in the sense in which this term is commonly understood. Child bearing was an accepted part of the parents' conception of matrimony. No contraceptive precautions were taken, and there was not even a fleeting thought of abortion. Yet the parents did not seem to know what to do with the children when they had them. They lacked the warmth which the babies needed. The children did not seem to fit into their established scheme of living. The mothers felt duty-bound to carry out to the letter the rules and regulations which they were given by their physicians. They were anxious to do a good job, and this meant mechanized service of the kind which

... we have seen almost twice as many patients, it emerges with even greater consistency and clarity.

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... creating a feeling of togetherness. But the fact remains that these parents are the kind of detached people that they are and that they would be known as such even if they had never had an autistic child. There is a resemblance between their make-up and that of their children, except that their aloofness has not reached the gross pro

100 fathers, 96 were high school graduates. Of these, 87 had been to college, 74 were college graduates, and 38 had postgraduate training. Two of the 4 who did not finish high school were immigrants from countries in which their poor economic condition precluded secondary schooling; the father of one of them became municipal band leader in a large city. As regards occupations, there were 31 business men, 12 engineers, 11 physicians (including 5 psychiatrists), 10 lawyers, 8 tradesmen, 5 chemists, 5 army or navy officers, 4 writers, 3 Ph.D.'s in the sciences, 2 Ph.D.'s in the humanities, 2 teachers, 2 rabbis, and one each a psychologist, a dentist, a publisher, a forester, and a photographer.

Of the mothers, 92 were high school graduates. Of these, 70 had been to college, 49 were college graduates, and 11 had postgraduate training. Not less than 70 had been active in a variety of endeavors, and some continued their occupations after marriage. There were 17 secretaries, 16 teachers, 6 business women, 6 librarians, 4 artists, 4 social workers, 3 writers, 3 nurses, 3 telephone operators, 2 psychologists, and one each a physician, a lawyer, a chemist, a Ph.D. in the humanities, a physiotherapist, and a laboratory technician.

To this day, we have not encountered any one autistic child who came of unintelligent parents. This fact gains added meaning if the personalities of the parents are subjected to careful scrutiny. Even though a study of this nature seems to elude the requirements for statistical deposition, it is safe to say that at least 85 per cent of the fathers and mothers present similar characterological features of a specific nature. Much caution has gone into the evaluation which resulted in the establishment of this percentage figure. It is further necessary to mention that in every one of the 100 cases at least one of the parents conforms to these characterological criteria.

As a rule, the parents of our autistic children are cold, humorless perfectionists. Most of them are not comfortable in the presence of people; they prefer reading, writing, painting, making music, or just thinking. They are polite and dignified people who are impressed by seriousness and disdainful of small talk. They describe themselves and their marital partners as undemonstrative. Matrimonial life is a rather cool and formal affair; there is no glamor of romance in premarital courtship, no impetuousness in postnuptial mating. The parents treat each other with faultless respect, talk things over calmly and earnestly, and give to outsiders the impression of mutual loyalty.

The parents' behavior toward the children must be seen to be fully appreciated. Maternal lack of genuine warmth is often conspicuous in the first visit to the clinic. Many of the fathers hardly know their autistic children. They are outwardly friendly, admonish, teach, observe objec-

tively but rarely step down from the pedestal of adulthood to indulge in childish play.

The void created by the absence of wholehearted interest in people is occupied by a devotion to duty. Most of the fathers are, in a sense, bigamists. They are wedded to their jobs at least as much as they are married to their wives. The job, in fact, has priority. Many of the fathers remind one of the popular conception of the absent-minded professor who is so engrossed in lofty abstractions that little room is left for the trifling details of everyday living. Obsessive adherence to set rules serves most of the parents as a substitute for the enjoyment of life.

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It can be said only of a few of the autistic children that they were *rejected* in the sense in which this term is commonly understood. Child-*bearing* was an accepted part of the parents' conception of matrimony. No *contraceptive* precautions were taken, and there was not even a fleeting *thought of* abortion. Yet the parents did not seem to know what to do with the children when they had them. They lacked the warmth which the babies *needed. The children* did not seem to fit into their established scheme of living. The mothers felt duty bound to carry out to the letter the rules and regulations which they were given by their physicians. They were anxious to be a good job, and this meant mechanized service of the kind which is rendered by an overconscientious gasoline station attendant.

This *picture of the* parents' personalities was drawn and reported originally on the basis of the observation of the first 20 cases. Now that we have seen almost *twice as many* patients, it emerges with even greater consistency and clarity.

It has been said that the described parental behavior toward the autistic children could be merely an understandable reaction to the offspring's isolation and lack of response. It is indeed easy to see that it would be impossible for anyone to maintain a satisfactory relationship with an infant whose aloneness frustrates all attempts at creating a feeling of togetherness. But the fact remains that these parents are the kind of detached people that they are, and that they would be known as such even if they had never had an autistic child. There is a resemblance between their make-up and that of their children, except that the aloneness has not reached the gross pro-

portions of a psychotic illness One is tempted to think of them as successfully autistic adults, in the sense that they do a creditable job in their chosen occupations and quite a few have attained sufficient recognition to be listed in some of the Who's Who compilations

CONCLUSIONS

1 Physical and laboratory examinations have failed to furnish any consistent clues regarding the constitutional background of early infantile autism

2 There is, in the families of autistic children, a remarkable paucity of psychoses and handicapping neuroses Considerably fewer than 5% have progenitors or other kin who can be so designated

3 The autistic children come from intelligent, sophisticated stock Not less than 94 per cent of the parents, both fathers and mothers, are high school graduates, 74 per cent of the fathers and 49 per cent of the mothers have completed college

4 The vast majority of the parents, though competent in their chosen vocations, are cold, detached, humorless perfectionists, more at home in the realm of abstractions than in the world of people They deal with their fellow men on the basis of what one might call a mechanization of human relationships They treat their children about as meticulously and impersonally as they treat their automobiles

5 The parents themselves have escaped the psychotic proportions of their offspring's aloneness and sterile obsessiveness It is possible to speak of them as successfully autistic adults

6 One is, therefore, led to think of a familial trend toward detached obsessive, mechanical living At the same time, it should not be forgotten that the emotional refrigeration which the children experience from such parents cannot but be a highly pathogenic element in the patients' early personality development superimposed powerfully on whatever predisposition has come from inheritance

7 These provocative findings warrant further research and classification

DISCUSSION

DR NOLAN D C LEWIS [New York N Y] Dr Kanner answered in part the question I had in mind If I understood him correctly there were no neuroses or psychoses among the parents of these autistic children but that a great majority of the parents were cold detached perfectionists who were at home in the realm of abstractions He indicated that these perhaps represented successful autistic adults

By that does he mean or could he assume that these parents are qualitatively schizophrenics of that variety designated by Kretschmer as the cold rigid perfectionist type of schizoid personality? Not psychotic in the usual sense of the term but of a schizophrenic constitution that has been arrested in its progress by certain compensations and adaptations that have been accomplished

CHAIRMAN WHITEHORN Dr H B Richardson asks Dr Kanner "In the admirable study of Dr Kanner, what is the evidence for a genetic factor, as distinguished from a familial factor, that is, the attitude of the parents?"

DR. LEO KANNER (Closing) Regarding Dr Lewis's question about what I mean when I say that the parents are successfully autistic adults I would say that these people function in society and in fact, function with such distinction that they are often at the top of scientific artistic or commercial enterprises Yet they have major problems which make them difficult parents as far as their children are concerned The outsider would be very much impressed by these people as well functioning and well adjusted adults Because of this, I do not think that we could possibly think of them as schizophrenic in terms of the schizophrenic psychosis

As for Dr Richardson's question, I do not believe that it is possible to make a sharp distinction between what is genetic and what is familial in terms of parental attitudes and their effect on the children In fact as I have indicated, some people have wondered whether the parents' reactions are not the effect that the children have on them because of the children's difficulties What we do have is a group of children presenting a special, unique, unduplicated syndrome and most parents, or the vast majority, do present this general picture Therefore, we must assume—as a matter of fact we must be convinced—that this matter in itself is not insignificant in the earl

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We have these data on hand and further efforts will show us what we can make of the data

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success of these efforts is the prolongation in life expectancy at birth, from for instance 38 3 years for a male birth and 40 5 for a female birth in 1850 in Massachusetts (9) to 65 5 years for a male and 71 years for a female in 1950 (2) A good deal of this increase in life expectancy is non specific, in that it affects all kinds of individuals But I suspect that a significant portion is selective involving not only those with gross defects referred to above but also individuals who are inherently less vigorous somatically in ways that modern medicine still has difficulty defining To the extent that physical defects and lack of resistance to the biological hazards of infancy and childhood are inherited—and again I will not stop for a detailed documentation of this point—we must recognize a second dysgenic influence

3 *Differential fertility*

It may be regarded as well established that the various occupational groups of many Western countries differ with regard to average performance on the so-called intelligence or aptitude tests To what extent this reflects innate differences between the individuals comprising these groups, and to what extent it is a consequence of cultural and educational factors is not now clear Most students of the subject although unwilling to reach any quantitative judgments would subscribe to the statement that *on the average* professional men for example are innately somewhat more intelligent than unskilled laborers I emphasize the qualification, *on the average* You are all familiar with the extensive overlap in the curves describing the frequency distribution of intelligence in these two groups

It is also well established that average fertility differs in many countries from one occupational group to the next with those groups whose average performance is lowest on the conventional intelligence tests tending to exhibit the highest fertility

There is finally a large body of data indicating that genetic factors are of importance in the individual s intelligence although here again for a variety of reasons the present data scarcely permit precise quantitat[illegible]
statem[illegible]
gene[illegible]
inte[illegible]

4 *Increasing exposure to ionizing radiation*

The fourth and last dysgenic influence to be mentioned is the increasing exposure of the human species to diagnostic therapeutic and military sources of ionizing radiation The available evidence indicates that even at relatively low doses this may be expected to increase the rate of mutation Inasmuch as most mutations are deleterious in their effects this can scarcely be expected to improve the genetic potentialities of man

CHAPTER XXIV

THE APPLICATIONS OF GENETICS TO HUMAN PROBLEMS

JAMES V. NEEL

THE BACKGROUND OF EUGENICS

For some years now there have been recognized four lines of evidence suggesting that the genetic potentialities of the human species were, at least in some cultures, subject to certain long-range influences which could only result in the deterioration of these potentialities. These so-called dysgenic influences may be summarized as follows:

1. War

The physical conflicts between individuals or small groups of individuals which must be assumed to have been the chief kind of strife in the early days of man, and from which the stronger or the more intelligent may usually be assumed to have emerged the victor, must be regarded as an instrument of natural selection. But at some point in the earth's history men banded together in groups which in their clashes with other groups were represented by individuals above the average in mentality and physique. To the extent that mental and physical attributes are inherited, the emergence of a group especially designated for military duties, i.e., an army, must be considered dysgenic.

2. *Relaxation of natural selection*

The relaxation of natural selection which has occurred in recent times is perhaps most obviously apparent in connection with the increased chance of survival of individuals with certain serious physical defects. No matter what one's concept may be of the organization of society in the world over 100,000 years ago, it is certain that persons with these serious physical defects were much less apt to live to reproduce then than now. Our compassionate society, and particularly Western culture with the value it places on the individual human life, is devoting an increasing proportion of its medical efforts to the well-being of individuals who because of congenital or constitutional defects formerly were liable to an early death. One index to the

Heredity Clinic, Institute of Human Biology, University of Michigan, Ann Arbor, Michigan.

In part the argument for our ignorance must proceed on an intuitive basis You cannot discuss problems of whose existence you are unaware—my intuitive feeling is that there are many such problems I hasten to add, in defense of the field of investigation with which so many of us are identified, that I believe tremendous strides have been made, and that we are really in a favorable position among those concerned with human biology But the fossil record suggests that man's evolution has extended over a period of roughly a million years What forces shaped man during that long period are still largely a matter of conjecture The serious study of human genetics is scarcely fifty years old Our horizons seem to be expanding on an exponential scale I for one am extremely reluctant on the basis of our present half knowledge to take even the initial steps toward what may be termed self-directed evolution Anyone surveying the problems of the world today cannot help but see numerous examples of what happens when man alters a natural equilibrium for proximate reasons without appreciating the ultimate consequences We deforest over graze and improperly cultivate the land and it disappears into the sea at a really appalling rate We decrease disease through sanitation the control of famine and medical advances, with the emergence of the so-called population problem We introduce an animal on the basis of inadequate ecological knowledge, and it becomes a pest whose control let alone eradication costs millions of dollars But, it may be argued the modern human geneticist is much too sophisticated to fall into such traps I wonder just how sophisticated we will appear fifty years from now

2 The second issue which deters me from a program of negative eugenics is what I propose to call the problem of the dividing line There are certain unfortunate individuals who genetically speaking *can never be regarded* as anything but a liability to the human species There are others who by equally objective standards possess an unusually high degree of that physical vigor and intellectual ability and stability which makes them an asset to the species The great majority of individuals however *fall into an intermediate category* We at the Heredity Clinic of the University of Michigan in the course of the genetic counselling which I will describe later are constantly impressed by how often one deals in various shades of gray rather than in black and white in considering the pros and cons of a course of human action based on genetic knowledge

Haldane (3 has particularly emphasized some of the pitfalls inherent in passing judgment on the relative value of an [illegible]

[illegible] can be graded (weight, intelligence muscular strength etc) there are six fundamentally different

THE EUGENICS MOVEMENT

The four distinct lines of evidence which I have just enumerated have been apparent to interested observers for many years Out of the concern of these individuals for the future of man has grown the eugenics movement, which may be broadly defined as an effort on the part of man to improve his heredity Two great subdivisions of the eugenics movement must be recognized namely so called positive eugenics aimed at encouraging the reproduction of those whom the eugenicist considers to be genetic assets, and so called negative eugenics aimed at discouraging the reproduction of those whom the eugenicist considers genetically unfit

I believe it fair to state that in the past the eugenics movement has derived a great deal of support perhaps the major source of its support—from those interested in nervous and mental disease This is really not surprising The papers of the past two days provide ample documentation of the importance of genetic factors in the etiology of nervous and mental disease This could not help but impress itself on those interested in the field In view of the difficult therapeutic problems presented by the diseases we have reviewed it is understandable that the idea of diminishing the amount of this disease in the next generation by measures aimed at limiting the reproduction of certain members of the present generation should find ready soil

One measure of the extent to which those concerned with diseases of the nervous system have entered into the field of negative eugenics emerges from a consideration of the so called eugenics laws of many states These laws are almost exclusively concerned with mental disease We shall return later to the question of the soundness of these laws

The contraindications to immediate eugenic action

Not everyone is satisfied that the evidence supports the thesis that genetically speaking the human species is on the verge of losing ground if indeed it has not done so already But if one grants that thesis then it must be admitted that eugenics has a strong emotional appeal The thought which I hope to develop in the remainder of this paper is that emotional appeal notwithstanding it is imperative that we proceed in this field with extreme caution For while there is no problem which in the long run has greater significance than the preservation of our genetic endowment there are few problems which are surrounded by a more thorny set of issues We turn now to a consideration of some of the issues

1 The first and scientifically most compelling reason for approaching eugenics with circumspection has to do with our relative ignorance of human genetics In part this ignorance is *demonstrable* Everywhere we turn in the field of human heredity we encounter important unsolved questions

sider the developments in the Third Reich which were justified in the name of eugenic procedures to appreciate what I mean. Such are the possibilities of genetic segregation and recombination that each of us may almost be said to constitute a unique genetic minority of one. What coalition of minorities will decide what other coalition of minorities is undesirable? I will grant that there are certain rare individuals exhibiting one or a combination of dominantly inherited pathological conditions concerning whose undesirability as parents there would be near unanimity of opinion, but how soon, again, do we leave that area of our knowledge where things are either black or white for the area where we are confronted with various shades of gray?

These remarks could be interpreted as an unwillingness to face certain social responsibilities because of a fear that our efforts miscarry, when that possibility is actually inherent in all forms of human social activity. To this it can be answered that there are different scales of necessity for action for different areas of social activity. The need for laws governing marriage, property holding, and the control of atomic energy is far more pressing than in eugenical considerations.

THE RATE OF CHANGE OF GENE FREQUENCIES

In my reluctance to espouse positive or negative eugenic measures at the present time, I find consolation for what some may term a too intellectual indecision in a consideration of the time scale on which the frequency of undesirable genes changes. Let us assume for the moment that certain arbitrarily designated proportions of individuals with serious diseases due primarily to simple dominant or recessive inheritance could be prevented each generation from reproducing. The numerical conse[illegible]

[illegible] inherited trait has a frequency either of 1 in 100 or 1 in 1000. We will assume that selection is in no way counterbalanced by mutation. Let us consider first a dominant trait. As shown in figure 75, complete selection against that trait, no matter whether it has an initial frequency of 1 in 100 or 1 in 1000, will obviously result in the elimination of that trait in a single generation. However, for a number of reasons complete selection against many dominant traits is unlikely; let us consider the results of 50 per cent negative selection. Now, as also shown in figure 75, the decline is quite appreciably slower. If next we consider a recessively inherited trait, the picture, as shown in figure 76, is very different. It requires almost five generations of complete negative selection to halve the frequency of a recessive trait with an initial frequency of one per cent, and

rankings possible. If we consider three genotypes which are being tested in three different environments with respect to some quantitative trait, the number of different rankings possible is 10,080. The general formula for calculating the number of ways in which m genotypes may be ranked in n environments is

$$\frac{mn!}{m!n!}$$

At $m = n = 10$, there are 7.09×10^{144} possible different patterns of response. Given, now, two or more different human genotypes with respect to some quantitative trait, and a number of possible environmental situations, it is apparent that for truly intelligent eugenic action we are required to know which of the many possible patterns of response to different environments these genotypes exhibit. I submit that it will be the work of a few years before we are on top of this problem with respect to any quantitative human trait.

The situation rapidly becomes more complex if we consider not a single characteristic but several at a time. In the simplest case of two criteria, two genotypes, and two environments, there are 72 different possible response patterns. The general formula for the number of different types of interaction is

$$\frac{(mn!)^k}{m!n!k!}$$

where m and n again represent the number of genotypes and environments, and k represents the number of different criteria under consideration.

Several years ago Muller (6) dealt with another aspect of this problem of the dividing line, when he drew attention to the fact that the average human is probably heterozygous for a minimum of eight semi-dominant genes with slight but deleterious effects when heterozygous. There are undoubtedly wide variations from individual to individual in the average number of these genes present. A person with a high concentration of such genes just as definitely may transmit a genetic handicap to his children as may an individual with a serious pathological trait due to a single dominant gene. How in any just scheme are the two to be equated? A policy of negative eugenics based on our present incomplete knowledge cannot help but be discriminatory, in the sense that it would single out for action the obviously handicapped, while failing to touch others even more handicapped but in less apparent ways.

3. The third thorny issue which interposes a barrier between myself and positive or negative eugenic action at the present time is concerned with the political and sociological implications of eugenics. One has only to con-

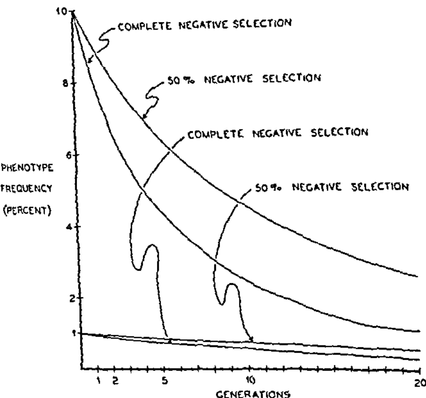


Fig. [illegible]. The effectiveness of 50 and 100 per cent negative selection against a trait determined by homozygosity for a single recessive gene, starting with an initial trait frequency of either 10 per cent or 1 per cent (modified by permission of Dr. Nils von Hofsten, Hereditas 37: 157, 1951)

In the foregoing I have dealt entirely with negative selection. It is apparent that with the exception of an undesirable trait due to a single dominant gene, even rather strong negative selection against certain types of inherited disease will not greatly alter the *frequency of the* genes responsible for the various diseases for several generations. Turning now to positive eugenics, since most of the desirable traits for which a society might wish to select appear, to the extent that they *are genetic*, to be determined by many genes, in general the changes in gene frequency which result from positive selection will be even slower. It is unlikely, then, that even what would be generally considered a strong program of positive and/or negative eugenics will greatly alter the genetic composition of the human species for the next several generations. Obviously this generalization does not include the possibility of drastic *measures directed* against relatively large segments of the population.

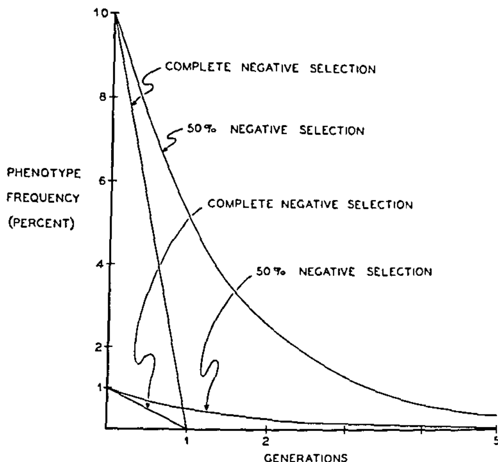


Fig. 76. The effectiveness of 50 and 100 per cent negative selection against a trait determined by a single dominant gene, starting with an initial trait frequency of either 1.0 per cent or 0.1 per cent. (Modified by permission of Dr. Nils von Hofsten, Hereditas 37: 157, 1951.)

correspondingly more generations at lower initial frequencies or with lesser degrees of negative selection.

Elsewhere I have summarized the available information concerning human mutation rates (7). There is reason to believe that the average rate of mutation per gene per generation in man is in the neighborhood of 1×10^{-5} and may well be somewhat higher. Figure 77, taken from von Hofsten's paper, illustrates what happens when negative selection is opposed by a mutation rate of 1:20,000. The effectiveness of the negative selection is now very seriously diminished.

Many undesirable traits, as for instance certain types of mental deficiency, may depend on the interaction of genes at two or even more different loci. It can readily be shown that under these circumstances the rate of change in gene frequency under negative selection is even slower than when only one gene is involved.

their children are poorly equipped to discharge their obligations as parents in our complex society. The first may be termed the genetic argument, the second the sociological. These two arguments have not always been kept separate. We will not be concerned here with the sociological argument, but will examine sterilization from the genetic point of view. In passing it might be pointed out that in addition to the categories of individuals mentioned above, the eugenic laws of seven states provide for the sterilization of habitual criminals, the laws of eight states for the sterilization of moral degenerates, and the laws of nine states for the sterilization of sexual offenders and perverts. The inclusion of such individuals in a eugenics law can only be regarded as an unfortunate carry-over from the early, uncritical days of eugenics.

Sterilization may be voluntary or involuntary. Where sterilization may legally be made compulsory, the law provides a number of safeguards for the individual concerned. While these safeguards are impressive, I cannot help but wonder whether the segment of the population involved is in a position to take advantage of them. Where sterilization is supposedly on a voluntary basis, the fact remains that release from the institution may sometimes be related to whether or not sterilization has been performed, a factor which certainly introduces an element of persuasion.

What now can we say concerning the effectiveness of present day sterilization procedures? At this point I should like to quote verbatim from a chapter in a forthcoming book by Dr. W. J. Schull and myself. I should add in passing that the foregoing presentation has already drawn heavily on that same chapter.

Figures compiled by the Human Betterment Association of America, Inc., reveal that in 1947 there were 1,232 official sterilizations in this country and in 1948, 2,922. These sterilizations involved the insane and the feebleminded in about equal numbers. During those same two years the number of children born in the United States was 3,699,940 and 3,535,068 respectively. It is conservatively estimated that at least 0.8 per cent of the population is feebleminded and at least 1.2 per cent develop the major psychoses which may be used as an indication for sterilization. Accordingly, it may be estimated in very round numbers (neglecting for the moment the lag between time of birth and time of sterilization) that about 3 per cent of the feebleminded and 2 per cent of the insane are each year permanently barred from parenthood as a result of present sterilization procedures. In many cases, however, these individuals have already produced one or more defective children.

The fact is often lost sight of that the insane and certain types of mental defectives have significantly decreased rates of reproduction. It is difficult to obtain accurate estimates as regards the insane. The situation

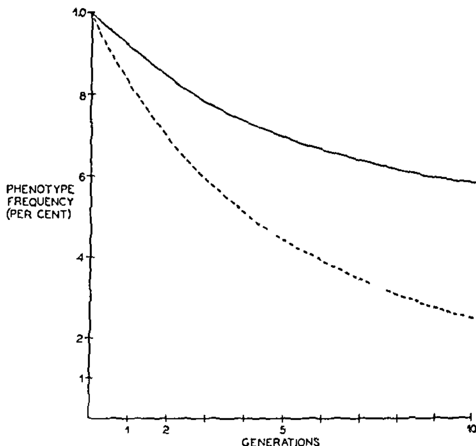


Fig. 77. A comparison of the effectiveness of complete negative selection against a recessive trait with an initial frequency of 1 per cent (a) when there is no mutation (broken line) and (b) when the mutation rate is 5×10^{-5} (solid line). (Modified by permission of Dr. Nils von Hofsten, Hereditas *37*: 157, 1951.)

A CRITIQUE OF EUGENIC STERILIZATION

I would like at this point to digress long enough to consider the so-called eugenic sterilization laws. Landman's (5) survey of the pertinent legislation in this country indicates that some 32 states have at one time or another passed what are often loosely termed "eugenic laws," although in five states these laws have subsequently been declared unconstitutional. Most of these laws were passed prior to 1930 in what may be termed the first flush of eugenic enthusiasm. The three classes of individuals who are particularly affected by sterilization laws are the feebleminded, the insane, and the epileptic. It is argued that inasmuch as these individuals tend to reproduce their kind—an argument to which we shall return later—it is sound preventive medicine to anticipate the birth of children who run a very significantly increased risk of becoming state charges. It is further argued that these unfortunate individuals, regardless of the caliber of

their children are poorly equipped to discharge their obligations as parents in our complex society. The first may be termed the genetic argument, the second the sociological. These two arguments have not always been kept separate. We will not be concerned here with the sociological argument, but will examine sterilization from the genetic point of view. In passing, it might be pointed out that in addition to the categories of individuals mentioned above, the eugenic laws of seven states provide for the sterilization of habitual criminals, the laws of eight states for the sterilization of moral degenerates, and the laws of nine states for the sterilization of sexual offenders and perverts. The inclusion of such individuals in a eugenics law can only be regarded as an unfortunate carry-over from the early, uncritical days of eugenics.

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What, now, can we say concerning the effectiveness of present day sterilization procedures? At this point I should like to quote *verbatim* from a chapter in a forthcoming book by Dr. W. J. Schull and myself. I should add in passing that the foregoing presentation has already drawn heavily on that same chapter.

Figures compiled by the Human Betterment Association of America, Inc., reveal that in 1947 there were 1,232 official sterilizations in this country and in 1948, 2,329. These sterilizations involved the insane and the feebleminded in about equal numbers. During those same two years the number of children born in the United States was 3,699,940 and 3,535,068 respectively. It is conservatively estimated that at least 0.8 per cent of the population is feebleminded, and at least 1.2 per cent develop the major psychoses which may be used as an indication for sterilization. Accordingly, it may be estimated in very round numbers (neglecting for the moment the lag between time of birth and time of sterilization) that about 3 per cent of the feebleminded and 2 per cent of the insane are each year permanently barred from parenthood as a result of present sterilization procedures. In many cases, however, these individuals have already produced one or more defective children.

The fact is often lost sight of that the insane and certain types of mental defectives have significantly decreased rates of reproduction. It is difficult to obtain accurate estimates as regards the insane. The situation

is more clear cut as concerns the mentally defective. Approximately 20 to 25 per cent of these unfortunates fall into the idiot and imbecile category. It is uncommon for such individuals to reproduce (1, 8). It may be presumed that this has been the case for centuries. Assuming that these individuals reproduce to no greater extent than those artificially sterilized reproduce prior to their sterilization, it is apparent that natural sterilization involves some seven or eight times as many people as the present legislative sterilization. There is evidence that the extreme degrees of mental defect are more often due to single genes than the borderline type of defect. We have seen earlier that negative selection is far more effective against traits determined by single genes than against traits determined by several genes. It follows that at present natural sterilization is many times more effective than legal sterilization. It further follows that present day sterilization programs are making a very small contribution to controlling the numbers of the insane and mentally defective.

The financial argument has often loomed large in discussions of sterilization programs. It is stated that sterilization is sound economically because it makes it possible to release individuals who would otherwise be institutionalized at public expense, and also prevents their (unborn) children from becoming public charges. The first argument is difficult to evaluate, for when such persons leave the institution they may become public charges in their local communities. The second argument is on somewhat clearer grounds. It has been estimated that in the case of the feebleminded each sterilization prevents an average of 2.5 births (10). Among the group on which this estimate was based, 36 per cent of the children born prior to sterilization were feebleminded (4). Assuming that these birth rates continue, then the sterilization of each 100 mentally deficient individuals results in the prevention of the birth of some 90 feebleminded children. The advocates of sterilization programs argue that any such decrease is a step in the right direction.

There are those in this country who are actively engaged in furthering the cause of sterilization on an expanded scale. There are undoubtedly individual cases in which sterilization is desirable as much on sociological as on genetic grounds. It would seem, however, that before any attempt gets under way to persuade large numbers of the population, either here or abroad, to submit to sterilization, it would be well to scrutinize the basic tenets carefully. Thus, as noted above, the three groups most commonly listed in state statutes as subject to sterilization are the feebleminded, the insane, and the epileptic. The empirical risk figures for these three groups are quite different. Whereas the empiric risk that a feebleminded parent will at any particular birth produce a feebleminded child is, as noted above, in the neighborhood of 35 per cent, the corresponding probability in the

case of epilepsy is currently placed at 3 to 6 per cent One cannot help but wonder about the wisdom of legislation treating these two diseases in a similar fashion or, for that matter, the reasons for including epilepsy originally when there exist so many other serious diseases with comparable or even greater empirical transmission figures

PRACTICAL APPLICATIONS OF GENETIC PRINCIPLES TO HUMAN PROBLEMS

There are then, reasons for serious reservations concerning the initiation of large scale eugenic programs as these are usually understood at the present time But you may then ask if not eugenics in the usual sense, then what if any are the immediate *practical* applications of such genetic knowledge as we have been reviewing these past several days? I stress the word *practical* since I am sure none would question the profound impact of genetic knowledge on our understanding of the forces that shape man, as this knowledge is pertinent to the fields of medicine psychology, sociology and so on

The practical applications of genetic knowledge are at present chiefly two-fold having to do with legal medicine and with genetic counselling In legal medicine genetics is of value primarily in parentage problems A consideration of this rather specialized branch of genetic knowledge would lead us beyond the confines of the present paper On the other hand something should be said about genetic counselling This may be defined as an attempt to render and interpret in an unbiased fashion a statement concerning the probability of the appearance (and course) of inherited disease in a particular individual As the problem usually presents itself, the parents of a child with disease which may or may not be genetically determined request a statement concerning the probability of a repetition in subsequent children Or an individual with a disease thought to be determined in whole or part by genetic factors requests information concerning the probability of the same trait appearing in a child Again with respect to an inherited disease of late onset as Huntington's chorea the question may arise as to the probability that a particular individual in a choreic family will develop the chorea

In the broad sense genetic counselling requires not only attention to the particular disease at issue but also to the entire genetic and even social background of the individuals involved In other word

Good genetic counselling requires attention to the total genetic picture rather than the single trait that brings the individual to the counsellor's attention

There can be no doubt that family planning is an integral aspect of the culture which we here share. The dominant factor is undoubtedly economic. However, somewhere on the list of other factors we find an item labelled "probable nature of offspring." Increasingly the laity *recognizes* that the appearance of disease in an individual is not always a blind caprice of fate, but sometimes the result of natural laws. It is a legitimate function of the geneticist to provide the interested individual with the best possible insight into these laws. Otherwise stated, people will plan families on the basis of what knowledge is available to them; better they have accurate genetic knowledge at their disposal than half truths and superstitions.

It has been our experience at the Heredity Clinic of the University of Michigan that not infrequently toward the end of an interview the individual involved requests an authoritative statement from the counsellor as to the desirability of having children. This may stem from confusion in the face of complex probabilities or an effort to shift responsibility for a possibly contentious decision. Such a recommendation leaves the field of genetic counselling as I have defined it and moves over into the area of eugenics. I must confess that the dividing line is sometimes poorly defined but we like to think we can maintain it.

I am sure that to many of you I appear to be straddling the fence, taking on the one hand a stand against premature attempts to influence the reproductive course of individuals with hereditary disease and yet advocating attempts to educate such persons concerning the pattern of transmission of the disease, attempts which cannot help but influence reproductive behavior in some cases. The dividing line between negative eugenics and genetic counselling as here defined, as I see it, involves the issue of whether *one attempts to impose a course of reproductive behavior upon the patient.* If in consequence of genetic counselling the patient and/or spouse reach a decision to limit family size, that is the patient's privilege. I would not attempt to influence such a decision either way. But to go one step farther, the laws of the state permitting, there are cases where I would be willing to be a member of a board of three certifying an individual for sterilization *at that individual's request.* For instance, just last week I saw a young woman with mild epiloia whose first and only child had a severe form of the disease. She was in the early stages of her second pregnancy. She and her husband were of average intelligence and moderate means. The first child had been a severe economic drain. Possessed of the facts, this couple requested a termination of the pregnancy with a sterilization of the wife. This would appear to be a valid request.

CLOSING REMARKS

Each year both the possibilities and the complexities of eugenics become more apparent. Our knowledge of the forces that have shaped man cannot

be described as anything but fragmentary. Our concepts of human mutation rates are based on the partial study of the behavior of a few dozen genes which may or may not be representative. Our ignorance of the kinds of selective factors which have been important in the past and are important today is profound. From the long range point of view there is nothing more important than the preservation, and perhaps the improvement, of those genetic attributes that have carried man to his favored position. And nothing I can think of could do the unfolding study of human heredity with all its broad implications, more harm than premature attempts to apply that knowledge in any dogmatic fashion to as complex an issue as man has ever tackled.

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